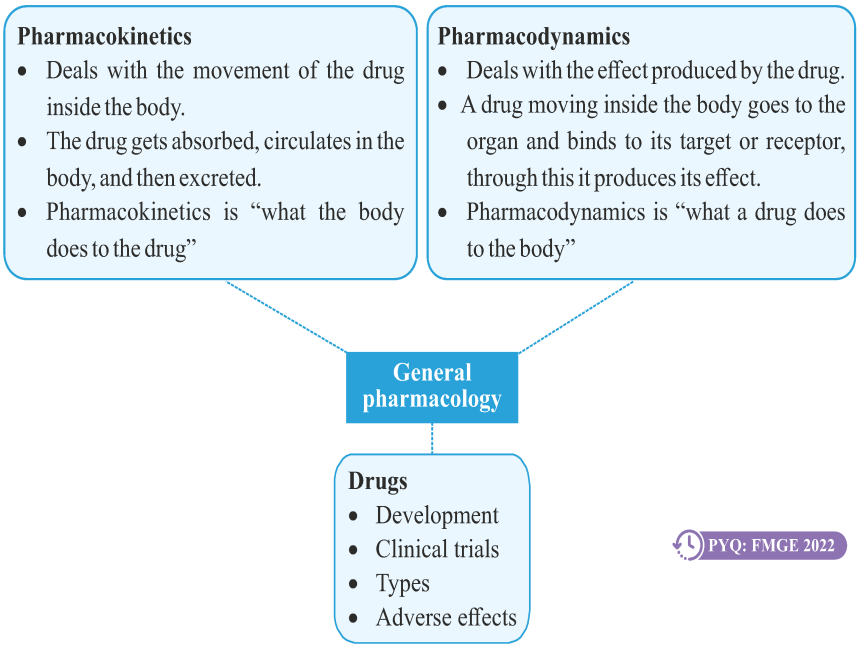
1 INTRODUCTION TO GENERAL PHARMACOLOGY

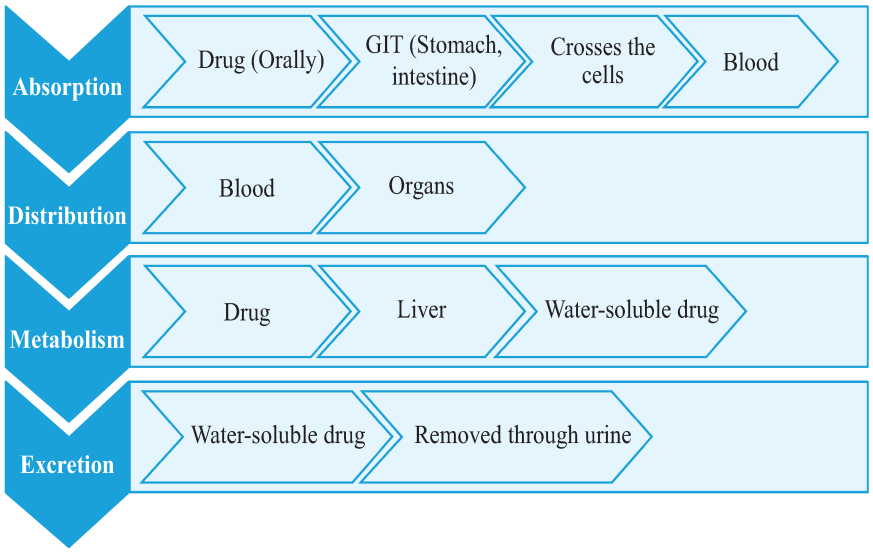


PYQ: FMGE 2022

2 PHARMACOKINETICS: ABSORPTION PART -1

Pharmacokinetics

- Pharma: Drug
- Kinetics: Movement of the drug inside the body
- Also known as the ADME study



- The drug is a foreign material, our body tries to remove drugs from the body through body secretions like Urine, sweat, saliva (as these are water-based water soluble drugs are excreted)

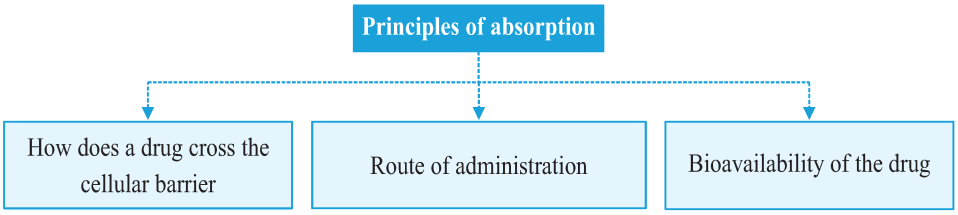
Primary Pharmacokinetic parameters	Secondary Pharmacokinetic parameters

• Absorption
  ○ Bioavailability (BA) of the drug- Amount of drug coming into the blood
• Distribution
  ○ The volume of distribution (Vd)
• Metabolism, Excretion
  ○ Clearance capacity (CI) – Power of the body to excrete drug
	• Half-life (t1/2)
	• Loading dose
	• Maintenance dose

Absorption of a drug

00:05:15

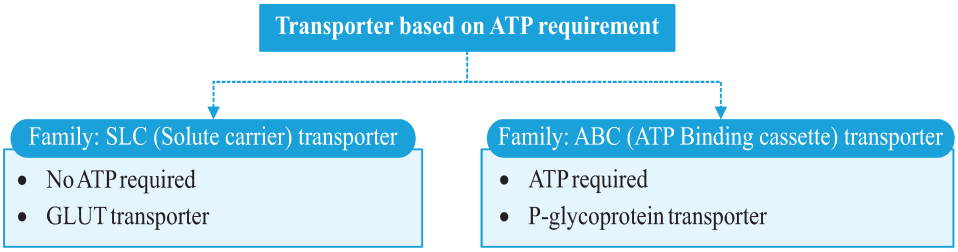
- Absorption is the cellular barrier, a drug has to cross to reach systemic circulation (blood veins)



How does a drug cross the cellular barrier

00:07:15

<table>
<tr><td>Simple/
Passive diffusion</td><td colspan="2">• The cell membrane is made of phospholipids that are fatty/lipophilic.
• Like dissolves like- Only a lipid-soluble drug dissolves in the cell membrane and crosses it
• No ATP/energy is required
○ Drug moves along the concentration gradient (High concentration to low concentration)
• Most drugs cross by simple or passive diffusion</td></tr>
<tr><td>Aqueous diffusion</td><td colspan="2">• Hydrophilic (Water soluble) drug crosses the cell membrane
• Aquaporins are present on the cell membrane, for carrying water-soluble drugs
• No ATP required
• Commonly seen in kidney/nephron: ADH (Antidiuretic Hormone) increases the synthesis of Aquaporins
• Drugs absorbed by aquaporins: Lithium</td></tr>
<tr><td>Filtration</td><td colspan="2">• Drugs cross the space between two cells known as Paracellular spaces
• No ATP required
• In the kidney, from Glomerular capillaries, blood gets filtered into nephrons
• Injection of insulin is given into the subcutaneous fat
○ Between subcutaneous fat, endothelial cells of capillaries are present, through which insulin gets absorbed into blood by Filtration</td></tr>
<tr><td>Endocytosis</td><td colspan="2">• Also known as Pinocytosis
• The cell changes its cell membrane, through a specific receptor and the drug enters the cell membrane
• Large proteins can be absorbed
○ Botulinum toxin (food poisoning)
○ Vitamin B12</td></tr>
<tr><td rowspan="6">Transport/
Carrier mediated
absorption</td><td>Facilitated diffusion</td><td>Active transport</td></tr>
<tr><td>• Pump: Specialized transporter
• The drug enters the cell with the aid of a pump</td><td>• Pump: Specialized transporter
• The drug enters the cell with the aid of a pump</td></tr>
<tr><td>• No ATPase enzyme</td><td>• ATPase enzyme present</td></tr>
<tr><td>• It does not require energy (ATP)</td><td>• Requires energy (ATP)</td></tr>
<tr><td>• Drug moves along the concentration gradient (High to Low concentration)</td><td>• Drug moves against the concentration gradient (Low to High concentration gradient)</td></tr>
<tr><td>E.g.
• GLUT transporter</td><td>E.g.
• $Na^{+}K^{+}$ ATPase transporter
• P-glycoprotein transporter</td></tr>
<tr><td>• 5 Fluorouracil gets absorbed through GIT</td><td>• Levodopa and methyldopa get absorbed through GIT by Dopamine transporters</td></tr>
</table>

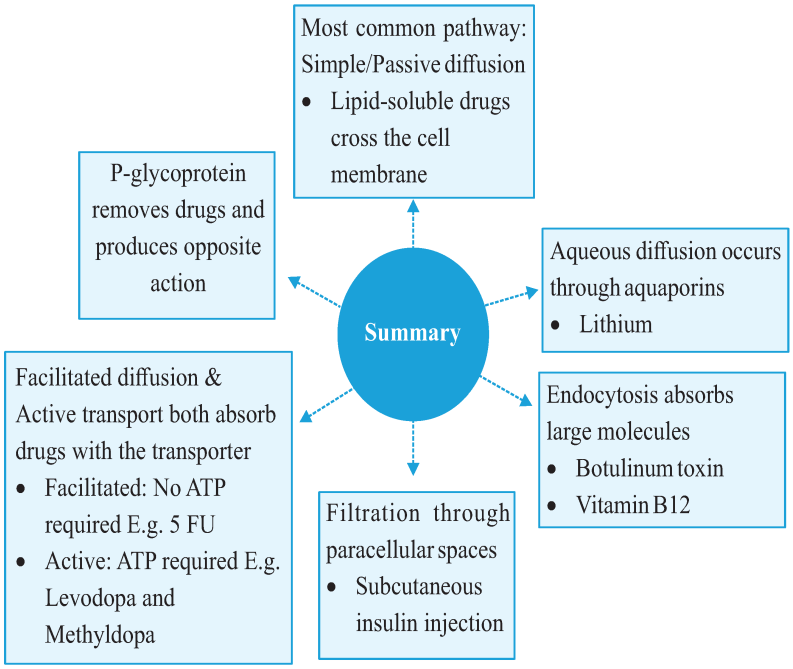


P-glycoprotein transporter 00:22:58

- **Also known as**
  - MDR (Multidrug Resistance) transporter
  - MRP (Multidrug Resistance Protein) transporter
- **Functions**
  - P-glycoprotein is an efflux transporter containing the ATPase enzyme
  - Its main function is to throw an already-absorbed drug from the cell
  - This inhibits absorption of the drug reducing its levels and effect.
  - P-glycoprotein is an enemy of the drug
- Location
  - GIT: Decreases absorption of the drug
  - Kidney: Increases urinary excretion of the drug
  - Liver: Increases bile excretion of the drug
  - BBB/placenta: Decreases entry of the drug
    → Protection
- Substrate of p-glycoprotein transporter
  - Any drug identified by p-glycoprotein is a substrate of p-glycoprotein transporter
  - E.g. Digoxin (heart failure treatment)

	P-glycoprotein inducer	P-glycoprotein inhibitor
Activity on p-glycoprotein	Increase activity of p-glycoprotein	Decrease activity of p-glycoprotein
Drugs	Rifampicin: anti-TB	Mnemonic: QVACKER • Quinidine • Verapamil • Amiodarone • Clarithromycin • Ketoconazole • Erythromycin • Ritonavir
Combined with Substrate of p-glycoprotein (Digoxin)	**Increases activity of p-glycoprotein** • Increase urinary excretion • Digoxin is excreted	**Reduces activity of p-glycoprotein** • Reduced urinary excretion • Increased plasma concentration of the drug • Toxicity of digoxin-Arrhythmias

Q. Which of the following drug inhibit ATP Binding cassette (INICET)
Ans. Verapamil



Simple/Passive diffusion

00:33:55

- Rate/Speed of diffusion is governed by Fick's law = CAP/T

  Fick's law = $\frac{CAP}{T}$
  - C: Concentration of drug
  - A: Area of cell membrane
  - P: Permeability coefficient
  - T: Thickness of cell membrane
- The rate of diffusion is directly proportional to the concentration of the drug and the Area
  - The higher the concentration of the drug, the more the drug enters the cell
  - The intestine has a large surface area, due to the presence of the brush border cells
- The rate of diffusion is inversely proportional to the thickness of the cell membrane

Simple diffusion depends on lipid solubility

00:37:35

Lipid soluble drugs	Water soluble drugs
Also known as Non-polar or Non-ionic drugs	Also known as Polar or Strong ionic drugs
If a drug is 100% lipid soluble, it crosses the cell membrane easily by simple/passive diffusion	If a drug is 100% lipid soluble, it does not cross the cell membrane easily by simple/passive diffusion
	• Oral Heparin ○ Anticoagulant (blood thinner) ○ Highly acidic ○ Not absorbed Orally • Aminoglycosides ○ Streptomycin, Gentamicin ○ Highly polar ○ Water soluble ○ Strong ionic ○ Not absorbed orally

- Weak ionic drugs
  - These drugs lie in between the range of water-soluble and lipid-soluble drugs
  - The solubility of a weak ionic drug depends upon the pK value

pK value 00:41:30

Definition

The pH at which the drug becomes 50% ionized and 50% non-ionized

Calculation of pK value

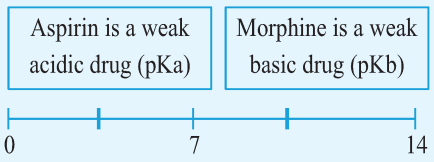
- pK value is calculated by the Henderson-Hasselbach equation
- $pK\,(drug) = pH\,(media) + Log\,\frac{(Non\text{-}ionic\ concerntration)}{(Ionic\ concentration)}$

Drugs with pK values

- Aspirin: 3.5
- Morphine: 8.5
- pK value may change based on the pH of the media
  - Stomach: pH is highly acidic (HCl): 0-1
  - Intestine: pH is highly basic (HCO3-): 8-9

pH scale

- Acidic: 0-<7
- Neutral: 7
- Basic: >7-15



- **In the same media, the drug becomes lipid-soluble**
  - If a weak acidic drug is kept in more acidic pH media, it becomes highly non-ionic or lipid soluble
  - If as weak basic drug is kept in more basic pH media, it becomes highly non-ionic or lipid soluble
- **In the opposite media, the drug becomes water-soluble**
  - If a weak acidic drug is kept in more basic pH media, it becomes highly ionic or water-soluble
  - If a weak basic drug is kept in more acidic pH media, it becomes highly ionic or water-soluble

Important Information

- Strong acidic or basic drugs are not influenced by the pH of the media
- Always remain Ionic

Importance of pK value clinically 00:50:35

- **Example: Aspirin (pKa: 3.5)**

In Stomach (pH: 0-1)	• Aspirin behaves as lipid soluble or non ionic drug • Cross cell membrane barrier • Enter stomach cells
Inside stomach cells	• pH similar of blood pH (7.2-7.4) • Ionised, water soluble • Does not cross cell membrane and does not enter circulation
Trapped inside stomach cells	Ion trapping
Destroy stomach cells	Gastric ulcers

Ionization and non-ionization of the drug based on pH of the media 00:53:55

- The change in pH of media by 1 changes ionization by 10% (log10)
- **Example: Aspirin (pKa: 3.5)**

Media pH	Lipid solubility/ non ionized	Water soluble/ ionized
3.5	50%	50%
2.5	90%	10%
1.5	99%	1%
0.5	99.9%	0.1%

- Basic drugs are absorbed from small intestine (Duodenum) >>> stomach
- Acidic drugs are absorbed from small intestine (Duodenum) > stomach
- Drug absorption mainly depends on area of cell membrane than pH
  - Intestine has brush border cells
  - All drugs are absorbed from small intestine due to the greater surface area
- Acidic drugs are absorbed in greater proportion from the stomach

Q. Antacids mainly reduce the absorption of?

A. Acidic drugs

B. Basic drugs

Ans. Acidic drugs

- Antacids are basic drugs
- Neutralise HCl in stomach neutralising the pH
- More acidic drugs are absorbed from stomach
  - Antiepileptics
    → Phenytoin
    → Valproate
  - NSAIDs
    → Aspirin

3 PHARMACOKINETICS: ABSORPTION PART -2

Routes of drug administration

Local route

- The drugs act locally and are not absorbed into systemic veins

Types of local route

Topical

- Applying a drug on some surface like skin, or mucous membrane (buccal mucosa, rectal mucosa, vaginal mucosa)

Into a closed cavity

Intra arterial

- The drug is administered into an artery.
- By blocking the artery above the site of injection produces, it produces a local effect.
- E.g. In the case of limb cancer, intra-arterial injection is used to avoid the side effects of anti-cancer drug

Intra-articular

- Administered into a synovial space
- To control inflammation corticosteroids are given in conditions like osteoarthritis, rheumatoid arthritis

Intravesical

- Administered into the bladder
- Anti-cancer drugs like Mitomycin and BCG vaccine are given for superficial bladder cancer (initial stage)

Intrathecal

- Administered into CSF
- Like methotrexate for brain cancer are given through intra thecal route

Intravitreal

- Administered into vitreous humor
- Vitreous humor is produced once in a lifetime and the drug comes in direct contact with retina when administered through this route.
- **E.g.** Ganciclovir used to treat CMV retinitis (CMV-cytomegalovirus)

Systemic route

00:06:20

- Drugs are absorbed into systemic veins
- the drug enters the venous circulation and is distributed to the rest of the body by the heart

Types of systemic route

Enteral route

- Through the GIT
- Oral route (drug absorbed from stomach and small intestine)
- Sublingual (Keeping a drug below the tongue)
- Rectal route

Parenteral route

- Routes outside the GIT

Injectable route

- IV (intravenous)
- IM (intramuscular)
- IO (intraosseous)
- ID (intradermal)
- SC (subcutaneous)

Non-injectable route

- Transdermal (through skin)
  - In topical route the drug will remain on the skin, in transdermal the drug absorbed into the skin
- Inhalational

Systemic route

Enteral route

00:09:14

1. **Oral route**

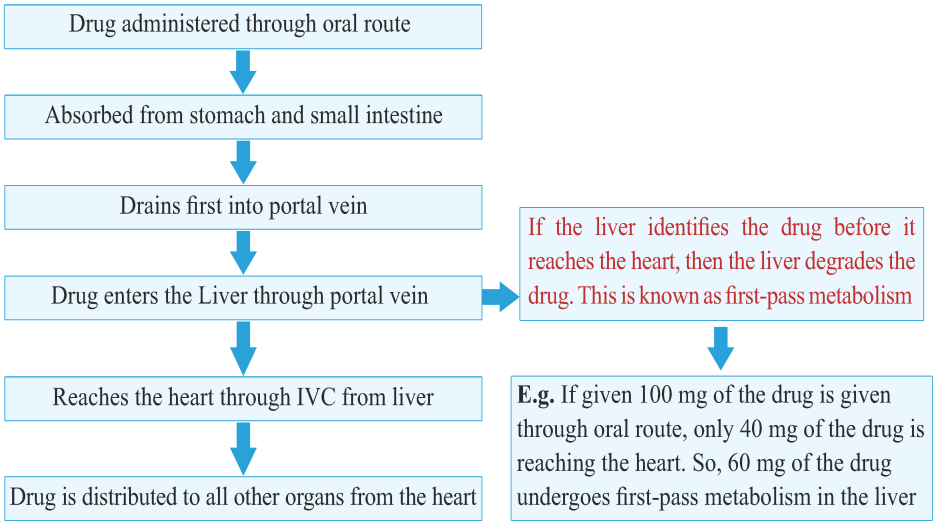
- The drug gets absorbed through the small intestine and stomach (more through the small intestine due to its greater surface area)

Advantages	Disadvantages
• Safest route ○ If harmful molecule gets absorbed, the liver and intestinal enzymes removes these toxins • Cheapest route • Preferred route	• Cannot be given in an unconscious patient • Cannot be given in an emergency • Unpredictable Bioavailability

- Drugs given through the oral route undergo First pass metabolism

First-pass metabolism

00:11:45



- The final amount of the drug reaching the heart is known as Bioavailability
- Other areas where first-pass metabolism occurs include walls of the stomach and small intestine
- First-pass metabolism of the drug reduces the bioavailability of a drug

Hepatic clearance-calculating fist-pass metabolism

00:15:40

- First-pass metabolism of the liver also known as Hepatic clearance

$$\text{Hepatic clearance} = \frac{CA - CV}{CA} \times \text{Hepatic blood flow}$$

  - CA = Drug in the portal vein
  - CV = Drug in the IVC

- Hepatic blood flow = When the drug is taken orally, it is continuously supplied to the liver by portal vein

- Amount of blood degraded by the liver is called the extraction ratio i.e., $\frac{CA-CV}{CA}$

- E.g. if 100 mg of the drug is given through oral route and 40 mg of the drug enters the IVC. The extraction ratio is,

  $= \frac{CA-CV}{CA}$

  $= \frac{100-40}{100}$

  = 0.6 or 60%

  = Hence the liver degrades 60% of the drug.

Q. If a drug has a very high first-pass metabolism in the liver. Is this given orally or not?
Ans. Either they are not given orally or they are given in very high oral doses.

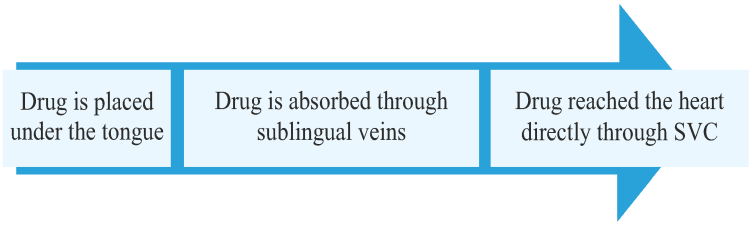
Drugs having high first-pass metabolism

Drugs not given orally	High oral dose drug
• Lignocaine	• Propranolol
• Fentanyl	• Morphine
• Natural steroids	• Verapamil
• Estrogen	• Pethidine
• Progesterone	• Salbutamol (Salbutamol is also given by syrups or tablets)
• Testosterone	• Nitrates
• Hydrocortisone	
• Aldosterone	

- Natural estrogen is not used in oral contraceptive pills because it has a very high first-pass metabolism
- Only synthetic estrogen known as ethenyl estradiol is given orally

Q. How to avoid (bypass) first-pass metabolism of the liver:
- By giving a drug by all other systemic routes except oral.
- Sublingual, rectal, and all parenteral routes

2. **Sublingual or Buccal route**



- Bypasses the first pass metabolism of liver
  - Example is sublingual nitrates
    - → Glyceryl trinitrate
    - → Isosorbide dinitrate
    - → It is the only drug for acute attack of angina
    - → All other anginal drugs for the prevention of angina

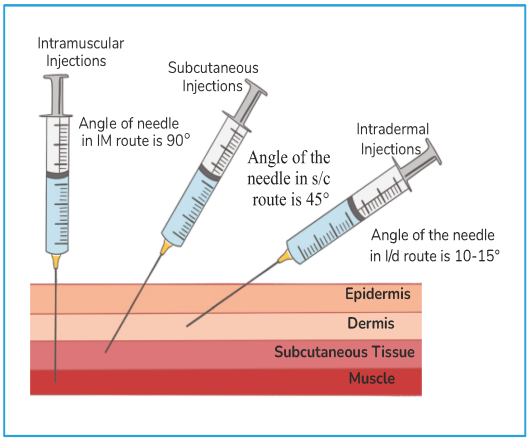
3. **Rectal route**
   - A drug given into the rectum is absorbed into a vein called an External hemorrhoidal vein
     - External hemorrhoidal vein is a tributary of IVC, hence the drug drains directly into the heart bypassing first-pass metabolism.
   - But, deeper in the rectum, the Internal hemorrhoidal vein is the tributary of the portal vein, thus the drug undergoes first-pass metabolism.
   - Example of rectal route: Rectal diazepam
     - It is the drug of choice for febrile seizures in children

Parenteral routes 00:30:30

- Injectable route

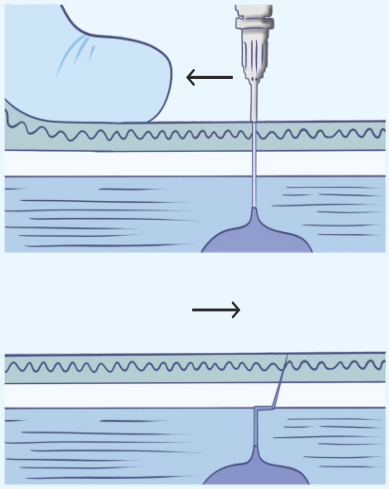
1. **Intravenous (IV)**
   - The drug is administered into a peripheral vein, and the vein directly goes to the heart
   - In the intravenous route there is no cellular barrier
   - IV route has 100 % bioavailability because there is no cellular barrier PYQ: INICET 2022
   - Dose titration of a drug is possible
     - It means, changing the dose slightly according to the effect of a drug , example:
     - Insulin produces hypoglycemia- reduce the dose
     - Insulin produces hyperglycemia- increase the dose
   - Dose titration done by two routes
     - Intravenous
     - Inhalational route (general anesthetics)
   - Intravenous is the route of choice in the emergencies, during surgeries
     → As intravenous route has predictable bioavailability

2. **IO (intraosseous)**
   - The drug is administered into a bone
   - The most common bone is the Tibia as it is a long bone, not covered by muscle, directly attached to the skin
   - IO route is preferred when IV route is not possible (during shock veins collapse)



3. **Intramuscular (IM)** 00:39:20
   - The drug is administered into the muscle
   - Water soluble drugs are rapidly absorbed due to the presence of a lot of blood vessels

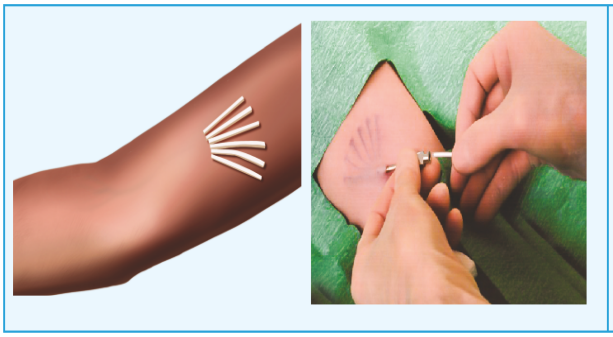
- DEPOT preparations
  - A rapidly absorbed drug can be converted into a slowly absorbed drug or a short-acting can be converted into a long-acting drug. by making a water-soluble drug into a lipid-soluble drug by attaching a lipid moiety
  - Example:
    - → Haloperidol (an antipsychotic drug) is a water-soluble drug, Fast onset of action.
    - → Attach one lipid moiety (undecanoate) to form an oily preparation thus making the drug longer acting
    - → This type of preparation is known as haloperidol decanoate
- Staining of subcutaneous fat
  - When IM injection is given, the fascia is punctured, and if the drug leaks back from this puncture site, it can lead to staining of subcutaneous fat.
  - E.g. Iron
  - Z (zigzag) technique



- When IM drug is administered, the skin is first pulled downwards, so that the fascia of the neighboring muscle is under the injection site.
- After administering, the skin is pushed back, and the fascia will be back to the normal position.
- This prevents the drug to be leaked from the puncture site avoiding staining of subcutaneous fat
- This technique is known as the zigzag technique
- Commonly used drugs
  - Iron dextran injection
  - Antipsychotic drugs

4. **Subcutaneous route (SC)**
   - The drug is administered by injection or a vacuum known as Dermoget.
   - Drug enters into subcutaneous fat, then absorbed into dermal blood vessels
   - Example:
     - Insulin
     - Low molecular weight Heparin

5. **Intradermal (ID)**
   - Given for allergic testing
   - Used in BCG vaccine



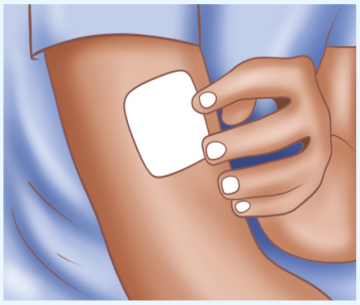
- Contraceptive implanted into subcutaneous tissue
- 6 rods of one contraceptive known as Levonorgestrel
- Known as Norplant which is implemented into subcutaneous fat

Transdermal route

00:48:30

Non injectable parenteral route

- Drug absorbed into the skin from a patch
- Through
  - Simple/passive diffusion
  - Absorption into dermal blood vessels



Dose of drug

- Depends on area of the patch and not on it's thickness
  - cm^2 or mm^2

Advantage

- Delivers constant amount of drug continuously around the clock
- Provides non fluctuating/constant drug level in the blood

Site of maximum absorption

- Posterior auricular area- on mastoid process behind the pinna
- Scrotum
- Face and neck
- Posterior auricular area > scrotum > face and neck

Site of least absorption

- Hyperkeratinized areas (skin is thick)
- Palms and soles

Transdermal patch	Indication
Nicotine patch	Smoking cessation
Nitrate patch	Long-term treatment of chronic angina
Hyoscine (scopolamine, anticholinergic drug)	Motion sickness
Diphenhydramine (antihistaminic drug)	Motion sickness
Selegiline	Depression
Rivastigmine patch	Alzheimer's disease
Rotigotine patch	Parkinson's disease
Clonidine	Long-term treatment of hypertension
Natural estrogen/progesterone	In Postmenopausal women as hormone replacement therapy

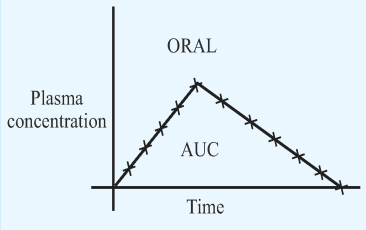
Inhalation 00:56:45

- Inhalational route can be local or systemic depending on the disease
- Example:
  - Bronchodilators given in asthma due to their local action on constricted bronchus
  - Anesthetic gases have systemic action as they are small molecules that enter the blood through alveoli and then cross the blood-brain barrier.
- Depending upon the particle size the drug enters the alveoli or remains in the bronchus
- To produce local action
  - Drug should have large particle size
  - 2-5 micron in diameter
- To produce systemic action
  - Drug should have a smaller particle size
  - < 2 micron in diameter

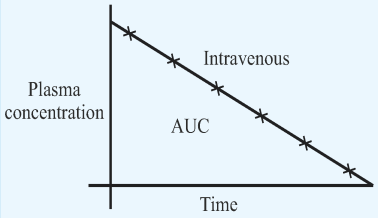
Bioavailability [F] 00:59:07

- Bioavailability is the fraction of the drug that reaches systemic circulation (veins)
- The unchanged form of drug reaching blood with time is Bioavailability
  - If drug is taken orally, it undergoes first pass metabolism
  - The drug that is not metabolized is unchanged form of drug
  - Drug takes certain time to reach blood after administration
- Bioavailability of intravenous route : 100%
  - IV route is taken as standard
    - → In calculating the bioavailability of other routes
- In remaining routes, bioavailability is < 100%
  - → Due to cellular barriers

Calculation of bioavailability- Concentration time graph



- If a drug taken orally,
  - The concentration of drug in blood increases slowly with respect to time and then it decreases
- In concentration time graph of that drug,
  - Area under the curve (AUC) – the total amount of blood that entered into circulation with time PYQ: INICET 2022



- Bioavailability of intravenous route : 100%
  - IV route taken as standard in calculating bioavailability of other route
- In remaining routes, bioavailability is < 100% due to cellular barriers
- If the same amount of the drug is given IV route
  - The concentration time graph gives downward straight line- Concentration decreases with time
  - AUC-higher (Total administered drug comes into blood)

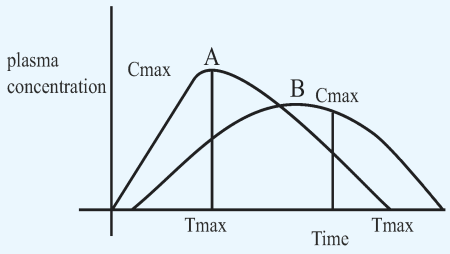
$$\text{Bioavailability [F]} = \frac{\text{AUC of concentration time graph (oral/any route)}}{\text{AUC of concentration time graph IV}}$$

Units of bioavilibility:

- Bioavilability has no units because numerator and denominator are same

AUC

- To calculate area under curve, AUC is divided into different segments
  - Each segment may have particular shape
  - In concentration time graph of oral drugs, the segments of AUG is in the shape of a Trapezium
- Area of trapezium is calculated
  - Add the area of each trapezium with each other
  - Gives AUC
- AUC calculated by Trapezoidal rule



- In concentration time graph,
  - The maximum concentration of drug in plasma – Cmax
  - The time at which drug attains Cmax is Tmax
- If drug A and B are administered
  - Both attain maximum concentration Cmax at Tmax
  - Among these A enters the blood faster or rapidly and B comes slowly into blood
  - Rapid and slow absorption is calculated based on Tmax
- Tmax: Rate of absorption (speed of absorption)
  - Drugs with small Tmax – rapid absorption
  - Drugs with high Tmax – absorbed slowly
- Cmax: maximum plasma concentration of a drug
- AUC: total extent of absorption (amount of drug entering plasma with time).

Sustained release preparation 01:12:15

- Conversion of fast absorbing drug into slowly absorbing or long-acting drugs
- This method of increasing the Tmax is called sustained release preparation or controlled release preparation
- Function :
  - Increase Tmax
  - Delay the rate of absorption of drug

- Conversion technique
  - Covering the tablet with inert polymer
  - Inert polymer – slow dissolution of drug
- The drugs that have fast absorption given for long term disease are converted into sustained release tablet

Sustained release drugs	Indication
Nifedipine • Have fast/sudden absorption • Due to low Tmax • Converted to sustained release preparation by increasing Tmax (rate of absorption)	Hypertension
Theophylline • Fast/sudden absorption • Converted to sustained release preparation to delay the rate of absorption absorption	Chronic asthma

Bio-equivalence

01:15:10

- Bio-equivalence - comparison of bioavailability of 2 brands of a same drug
  - Also known as generic drugs
- Example:
  - Crocin- paracetamol 500 mg have bioavailability of x
  - Dolo- paracetamol 500 mg have bioavailability of y
  - Comparison of bioavailability of these 2 brands of paracetamol is bio-equivalence
    - → Exactly same Bioavailability is difficult to achieve
    - → Slight variation is acceptable
- **Acceptable level**
  - If the other brand is getting absorbed upto 125% more and 80% less
  - 25% variation between 2 brands of same drug is acceptable
  - If two brands of a drug have variation in bioavailability within acceptable range these brands are called bioequivalent to each other
  - Brands can be interchanged
- **Exception:** phenytoin
  - Does not follow concept of bio-equivalence
  - Two brands of phenytoin
    - → Dilantin
    - → Eptoin
  - A small increase in absorption of phenytoin leads to toxicity
  - A small decrease in absorption – rebound seizures
  - Even 80-125% variation in bioavailability is not acceptable for phenytoin
  - So all brands of phenytoin are bio-inequivalent to each other
    - → Never change the brands of phenytoin
    - → Even small variation is harmful for the patient

4 PHARMACOKINETICS: DISTRIBUTION

Introduction

- The movement of a drug into the target organ produces a therapeutic effect.
- The movement of a drug into unwanted organs has an adverse effect

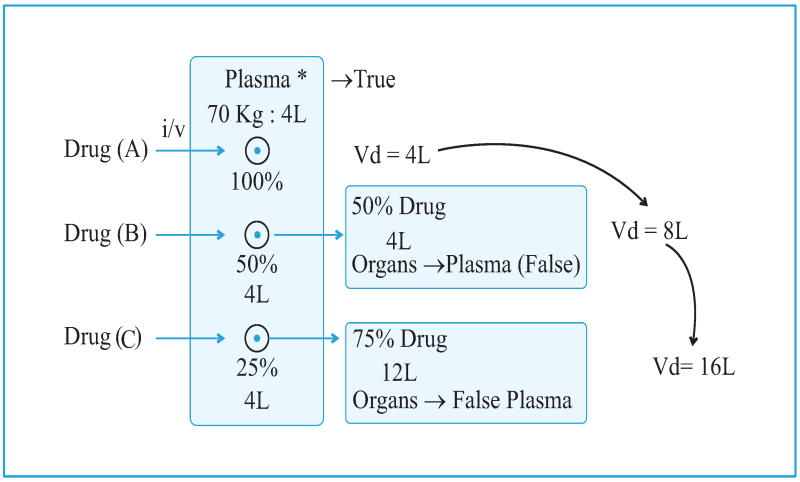
Volume of Distribution (Vd or aVd)

00:01:45

- Vd is false/apparent volume of plasma
- **Definition:** Volume of plasma (ml) required to contain a drug in equal concentration as that of plasma

Scenario

- Assume a 70 kg individual contains 4 liters of plasma and the drugs A, B, and C are administered through IV.
  - **Drug A:** The whole drug is absorbed into the plasma and does not move into the organ. So, 4 liters of plasma is required to contain this drug. Vd = 4 litres.
  - **Drug B:** 50% remains in plasma (true plasma, 4 liters), and 50% moves into the organ (false plasma, 4 liters). Vd = 8 litres.
  - **Drug C:** 25% remains in plasma (true plasma, 4 liters), and 75% moves into the organ (false plasma, 12 liters). Vd = 16 liters.



- **Formula to calculate Vd**

$$Vd = \frac{\text{Dose given (i/v)}}{\text{(actual) plasma conc.}}$$

- Units of Vd
  - Liters/ml
  - However, using liters/kg of body weight, Vd is equal regardless of age group and weight.
  - As plasma concentration reduces, Vd increases, indicating that the drug is moving out of the blood vessel.

Factors modifying Vd

Drug properties

- Lipid solubility (pK) ∝ Vd
- Plasma protein binding 1/∝ Vd

Physiological properties

- Age, gender, pregnancy
- Diseases
  - Liver diseases decrease albumin production → increased Vd and toxicity
  - Kidney disease results in albuminuria → increased Vd and toxicity
- Hemorrhage, burns, shock → increased toxicity

Q. There is a drug known as Warfarin, which is highly lipid soluble and 99% protein (albumin) bound. What will be its Vd?

Ans. Low Vd → plasma protein binding is always predominant over lipid solubility when determining Vd.

Plasma Proteins

00:19:25

Albumin

- Basic protein → binds to acidic drugs
  - Aspirin (NSAIDS)
  - Anti-epileptics
  - Barbiturates
  - Warfarin
  - Acetaminophen
  - Sulfonamides / Sulfonylurea

α_1 Acid Glycoprotein

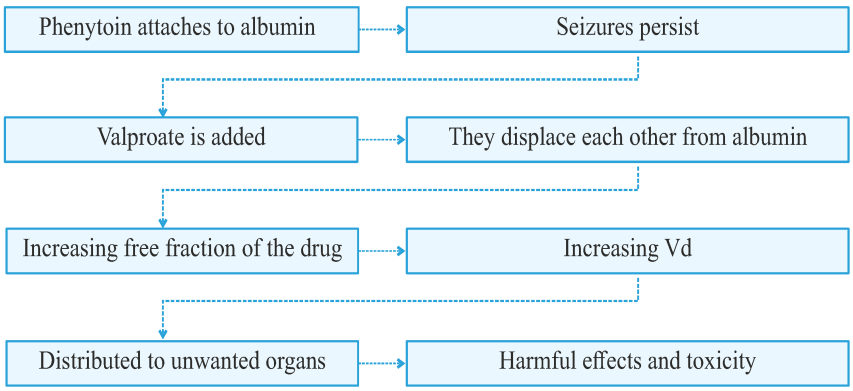
- Acidic plasma protein → binds to basic drugs
  - Anti-Arrhythmics
  - β-blockers
  - Calcium channel blockers
  - Opioids
  - Imipramine
  - Lignocaine

Importance of plasma protein binding

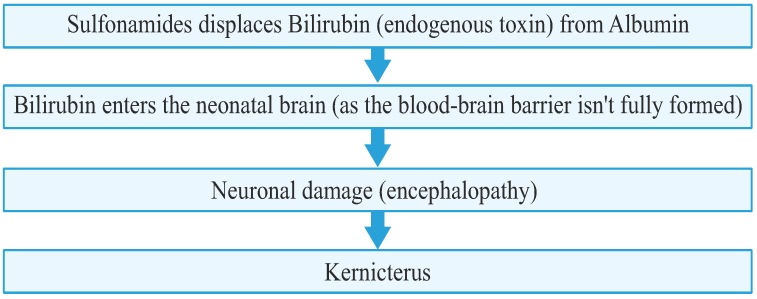
Plasma protein binding of a drug is non-specific and reversible, leading to drug displacement, which can result in a toxic effect.

Examples of Drug displacement from plasma proteins

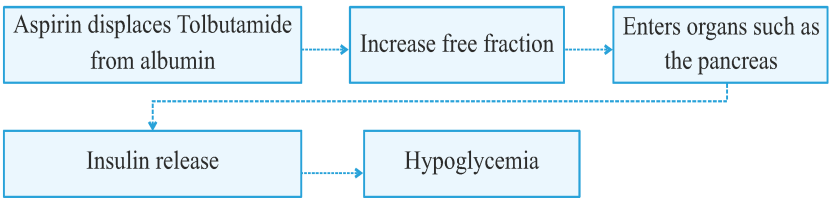
Q 1. All antiepileptics increase each other toxicity?



Q 2. Sulfonamides (Cotrimoxazole) is contraindicated in neonates and the last trimester of pregnancy.



Q 3. Does aspirin cause hypoglycemia with tolbutamide (sulfonylureas)?



Hemodialysis (HD)

00:32:15

- Employed in the treatment of drug poisoning
- Process,
  1. Take out the poisoned blood of the patient
  2. Filter the drug through a semipermeable membrane

Q. If a drug has high Vd, there is no role of hemodialysis. Why?
Ans. High Vd drugs are not present in plasma. E.g. Digoxin (450L of plasma)

Q. If a drug has low Vd and high plasma protein binding, will hemodialysis be allowed?
Ans. No. Plasma protein will not allow the filtration of a drug. E.g. Warfarin (99% Albumin bound), Verapamil

Q. If a drug has low Vd and low plasma protein binding (free form), is hemodialysis allowed?
Ans. Yes

Drugs that require hemodialysis

Do hemodialysis	No role of hemodialysis
• Barbiturates • Lithium • Alcohols • Aspirin • Salicylates • Theophylline	• Amfetamine • Verapamil/ Warfarin • Organophosphate • Imipramine (TCA: Tricyclic Antidepressant) • Digoxin • Amiodarone • Benzodiazepine (Diazepam) • Chloroquine→ overall highest Vd

- Chloroquine has the highest Vd, 1500 liters of plasma, depositing in almost all organs when ingested.
  - E.g. Chloroquine deposits in concentric rings in the retina, a condition called Bull's eye retinopathy, resulting in permanent blindness.

Bull's eye retinopathy

Redistribution

00:41:20

- **Drugs that exhibit redistribution:** Thiopentone, fentanyl, general anesthetics
- Redistribution is shown by highly lipid-soluble drugs
- Main site of action: brain

Highly lipid soluble drug- Thiopentone

↓

Thiopentone enters the brain first as it is highly perfused and has a large blood supply

↓

Causes unconsciousness in 2 to 5 minutes

↓

Thiopentone enters the bloodstream from the brain

↓

Redistribution - Thiopentone is deposited into fats instead of being excreted via urine.

↓

After redistribution, plasma content decreases

↓

The action of thiopentone on the brain will end.

Q. The action of Thiopentone is terminated by:

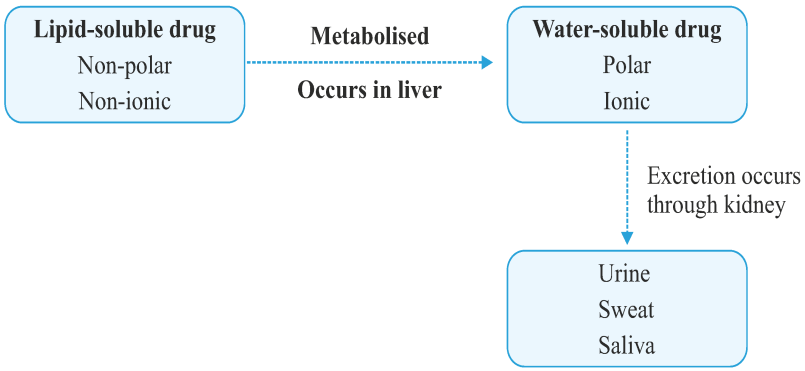
A. Redistribution into fats

B. Elimination into urine

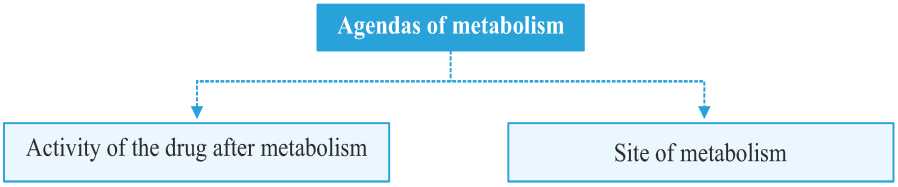
5 PHARMACOKINETICS: METABOLISM

- Metabolism is also known as Xenobiotics (Xeno: Foreign substance/ drug and Biotics: chemical reaction inside the body) or Biotransformation

Definition of metabolism



- Metabolism + excretion = Elimination of drug



Activity of the drug after metabolism

00:03:20

1. Active drug undergoes metabolism to give an inactive drug terminating its action.
2. Active drug undergoes metabolism to give another active form (metabolite)
3. Inactive drugs (Prodrugs) undergo metabolism to give active drug

Examples of active drug to another active drug	Examples of prodrug to active drug

• **Fluoxetine → Nor-fluvoxetine**
  ○ Longest acting antidepressant
  ○ Forms another metabolite that acts for a longer duration
• **Allopurinol → Oxypurinol**
  ○ Oxypurinol is developed separately for gout
  ○ Oxypurinol AKA: Alloxanthine
• **Diazepam → Oxazepam**
  ○ Oxazepam is developed separately
  ○ Does not go to the liver
  ○ Safer than diazepam
• **Spironolactone → Canrenone**
• **Codeine → Morphine**
• **Primidone → Phenobarbitone**
	• **Prednisone → Prednisolone**
	• **Levodopa → Dopamine**
	• **ACE inhibitors (-pril) → active form ends with -prilat**
	  ○ Enalapril → Enalaprilat
	  ○ Fosinopril → Fosinoprilat
	  ○ Trandolapril → Trandolaprilat
	• **Sulfasalazine → in the intestine converts to**
	  ○ **Sulfapyridine**
	  → Treatment of Rheumatoid arthritis
	  ○ **5 ASA (Amino salicylic acid)**
	  → Treatment of UC (ulcerative colitis)
	• **Mycophenolate mofetil → Mycophenolate**
	  ○ Immunosuppressive drug

	○ Given in organ transplantation • **Aciclovir/ Ganciclovir → attach to a phosphate group (active)** ○ Against herpes group of virus ○ Block DNA synthesis • **Carbimazole → Methimazole** ○ Methimazole is available as a separate antithyroid drug • **Clopidogrel/Prasugrel → Active form** ○ Antiplatelet drugs • **Dipivefrin → Epinephrine (in eyes)** ○ Glaucoma

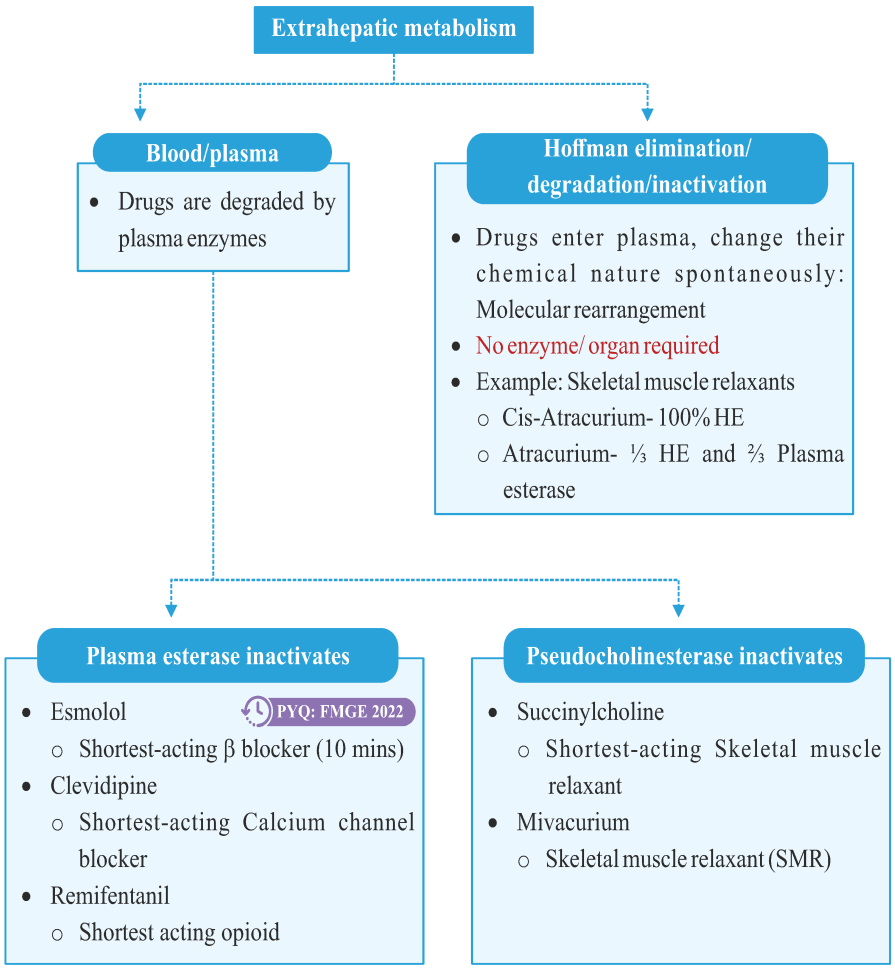
Important Information

- All ACE inhibitors are prodrugs except Captopril and Lisinopril

Site of Metabolism

00:14:30

- **Hepatic metabolism-** The most common site of metabolism is the liver
- **Extrahepatic metabolism-** Some drugs undergo metabolism outside the liver



Q. Which skeletal muscle relaxant is safe in hepatic failure?

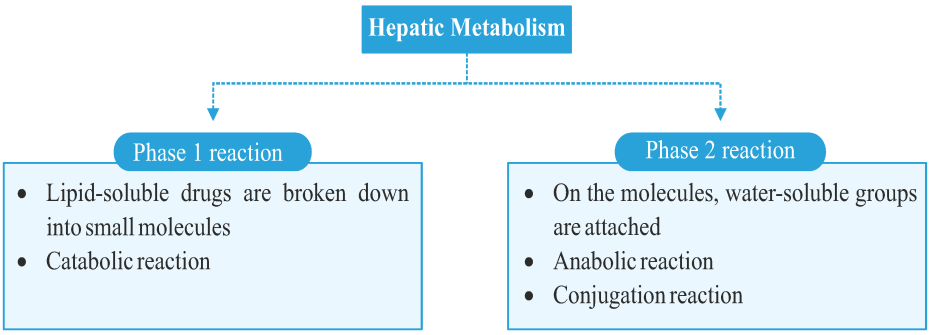
A. Atracurium

B. Succinylcholine

Ans. Atracurium

- Does not require any organ or enzyme for metabolism
- Used in most surgeries
- Even though succinylcholine is not degraded by the liver, as pseudocholinesterase is synthesized in the liver leading to its deficiency in hepatic failure
  - Succinylcholine is not metabolized causing respiratory paralysis due to its toxicity.

00:24:00



Differences between Phase 1 and 2 reactions

	Phase 1 reaction	Phase 2 reaction

Activity of the drug	• Drugs convert into
	  ○ Active form
	  ○ Inactive form
		• Converts into inactive form only
		• Except: Morphine, Minoxidil
		  ○ Converted into an active form
		• Enzymes transfer polar groups

Type of reaction	• Oxidation
	  ○ CYP-450 enzyme
	• Reducntion
	  ○ CYP-450 enzyme
	• Hydrolysis
	  ○ Hydrolase enzyme: Esters
	• Deamination
	  ○ Adenosine deaminase: Purines (Adenosine)
	• Dehydrogenation
	  ○ Alcohol dehydrogenase: Alcohols
	• Cyclization
	  ○ Proguanil
	• Decyclization
		• Glucuronide conjugation
		  ○ Uridine Di-phosphate glucuronyl transferase (UDP-GT)
		• Acetylation (add Acetyl group)
		  ○ Acetyltransferase: SHIP drugs
		• Methylation
		  ○ Methyl transferase
		• Glycination
		• Sulfation
		• Glutathionylation
		  ○ Paracetamol

Most common reaction	Most drugs undergo oxidation and reduction	Most drugs undergo Glucuronide conjugation

Site of reaction	• Smooth Endoplasmic Reticulum (SER)
	  ○ Also known as Microsomes
	• Microsomal reactions
		• Outside SER
		  ○ Non-microsomal reactions
		• Except: Glucuronide conjugation
		  ○ Microsomal reactions

Important Information

- Prodrugs are converted into active form by Phase 1 reaction.
- Most of the drugs are metabolized by Microsomal system

UDP-GT deficiency

- **Conditions**
  - Crigler-Najjar syndrome
    → UDP-GT attaches glucuronide to bilirubin and bilirubin becomes water-soluble and excreted out in the urine
    → Deficiency of UDP-GT deposits bilirubin in the body- Jaundice
  - Gilbert Syndrome
- **Drugs that require UDP-GT for removal from the body**
  - Irinotecan, anticancer
    → Toxicity: Bone marrow cancer → Neutropenia
  - Atazanavir, anti-HIV
    → Hyperbilirubinemia
- Irinotecan, Atazanavir are contraindicated in Crigler-Najjar and Gilbert syndromes

Differences between Microsomal and Non-microsomal system

	Microsomal system	Non-microsomal system
Location	• Inside SER	• Outside SER
Number of drugs metabolized	• Most of the drugs	• Few drugs
Activity of the system	• Increased/ decreased by drugs ○ Enzyme inducers ○ Enzyme inhibitors	• Not affected by drugs
Genetic polymorphisms	• Seen	• Seen

CYP-450 enzymes

00:43:00

- Required for phase 1 reaction

Nomenclature

- CY: Cytochrome
- Cyto: Inside cell
- Chrome: colored enzyme
- Contain heme pigment
- Heme is also seen in Hemoglobin, myoglobin
- P: Peak light absorption
- 450: at 450 nm

Spectrophotometry is used to identify enzyme

- **Light is** passed through enzyme and all wavelengths are reflected.
- 450 wavelengths is absorbed and seen as a peak on monitor

Genetic polymorphisms

- One gene can make different quantity and types of enzymes

Naming a CYP enzyme

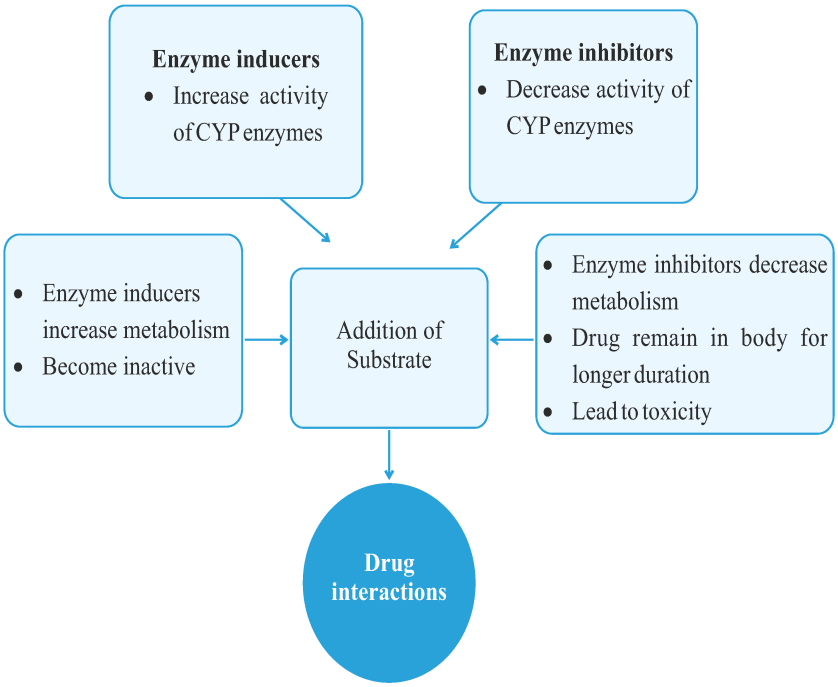
- E.g. CYP3A4
  - 3: number of the gene making CYP enzyme (Family of CYP)
  - A4: Isoform/Subtype of CYP

Important Information

- One gene hypothesis: One gene can make one type of enzyme- This hypothesis was rejected
- One gene can make one mRNA
  - Different types and quantities of enzymes are produced
- More than 75 enzymes make CYP enzymes

CYP type	Substrate (drugs metabolized by CYP)
CYP1A2	Theophylline, Clozapine
CYP2C9 (earlier known as CYP2C8) • Least quantity • Dye to genetic polymorphism	Phenytoin, Warfarin • Saturation kinetics is seen
CYP2C19	• Clopidogrel (Antiplatelet drugs) • Azoles (Antifungal drugs) ○ Voriconazole ○ Ketoconazole • PPIs (Proton Pump Inhibitors) ○ Omeprazole ○ Pantoprazole
CYP2D6	• β-blockers (Propranolol) • Antiarrhythmics (Quinidine) • Tamoxifen • TCA (Tricyclic Antidepressant) • SSRIs (Antidepressants) • Opioids (Codeine) • Neuroleptics (Antipsychotics) ○ All are metabolized except, Clozapine which is metabolized by different CYP
CYP2E1	• Paracetamol
CYP3A4 (maximum quantity in our body) • Responsible for metabolism of >50% drugs	Most drugs are metabolized • Astemizole ○ Antihistaminic drug • Benzodiazepine (Midazolam) • Cyclosporine/ Tacrolimus ○ Immunosuppressive drugs

	• Diltiazem/ verapamil
	  ○ Calcium channel blockers
	• Estrogen
	  ○ Oral contraceptive pills
	• Fexofenadine/Terfenadine



Enzyme inducers

- **Mnemonic: GRASS**
- Griseofulvin: Antifungal
- Rifampicin: Anti TB
- Antiepileptics
  - Phenytoin
  - Carbamazepine
  - Phenobarbitone
  - Except Valproate is an inhibitor
- Alcoholism (Chronic)
  - Enzyme is rapidly metabolized
  - Acute alcoholism: enzyme inhibitors
  - Chronic alcoholism: enzyme inducers
- Smoking
  - Metabolism of nicotine increases
- St. John worts
  - Plant eaten in western or European countries to treat depression
  - May lead to interaction

Enzyme inhibitors

- **Mnemonic: COKE in Gallon Contain Artificial Preservatives**
- Cimetidine: Antihistaminic drug
- Omeprazole: First PPI
- Ketoconazole: First antifungal drug
- Antibiotics: Erythromycin, Clarithromycin
- Isoniazid: Anti TB
  - Inhibit all CYP enzymes
  - Except CYP2E1
  - Inducer of CYP2E1
- Grapefruit juice: Furano coumarins
- Ciprofloxacin
- Acute alcoholism
- Protease inhibitors (Anti HIV)
  - Ritonavir

Important Information

- For enzyme inhibition only one dose of the drug is required, but enzyme induction requires 7-14 days.

Drug interactions

01:03:45

Estrogen

- **Oral contraceptive pills**
- **CYP3A4** inactivates estrogen
- Scenario: If a woman taking OCP is infected with TB and she is prescribed Rifampicin
  - Rifampicin is a CYP enzyme inducer and increases CYP activity
  - Estrogen rapidly gets inactive leading to contraceptive failure

CAT drugs

- Cisapride (Constipation)
- Astemizole
- Terfenadine
- These drugs are substrates of CYP3A4 and convert them into inactive form
- Scenario: Along with the CAT drugs, Erythromycin/Ketoconazole is prescribed
  - Erythromycin and Ketoconazole are CYP inhibitors and degradation of these drugs is inhibited
  - They increase the toxicity of CAT drugs
  - On heart, increase QT interval- Torsades de pointes
- CAT drugs are banned due to erythromycin and ketoconazole

Clopidogrel

- **Clopidogrel is a prodrug converted to an active form by phase 1 reaction**
- Substrate of CYP2C19
- Clopidogrel on activation is an antiplatelet drug given for MI and Stroke
- Scenario: Clopidogrel has a side effect of bleeding in the stomach for which Omeprazole may be prescribed
  - Omeprazole has a maximum CYP inhibitor action decreasing the activity of clopidogrel and increasing the risk of MI and stroke increase
  - Clopidogrel should be avoided with omeprazole
- Rabiprazole and Pantoprazole have low CYP inhibitor action

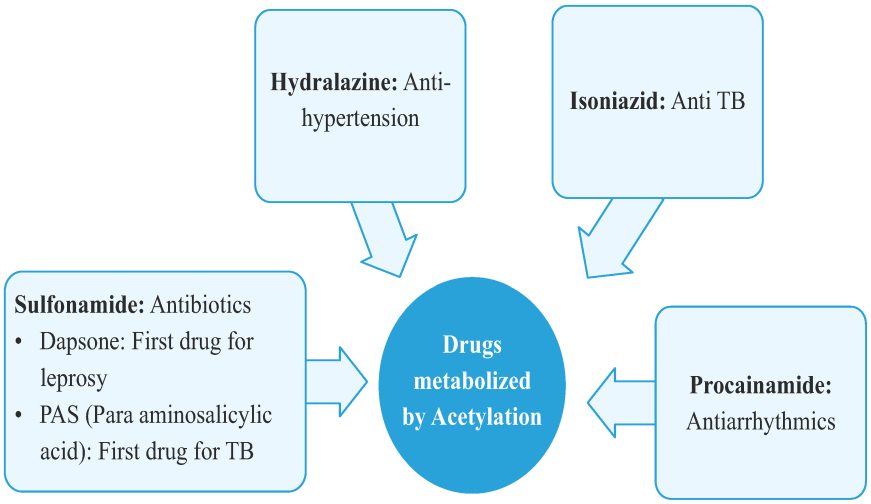
Tamoxifen

- **Tamoxifen is a prodrug and on activation, it is converted to Endoxifen used as an anti-cancer drug** in breast cancer
- Substrate of CYP2D6
- Scenario: Cancer patients suffer from depression and antidepressants like SSRI: Fluoxetine may be prescribed
  - Antidepressants like Fluoxetine inhibits CYP2D6 reducing the effect of tamoxifen and increasing the chances of breast cancer metastasizing

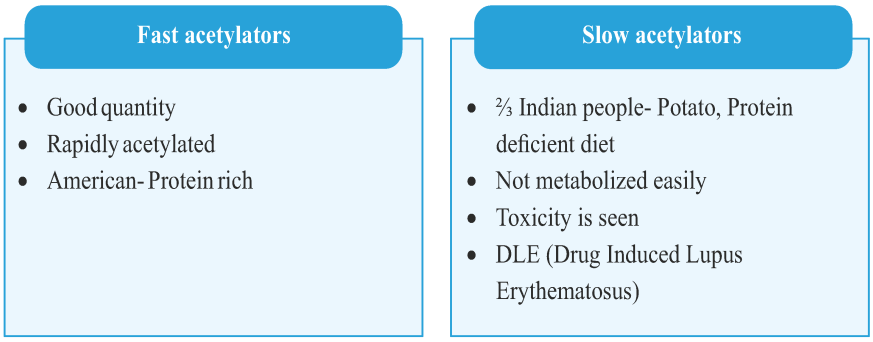
Drugs metabolized by Acetylation

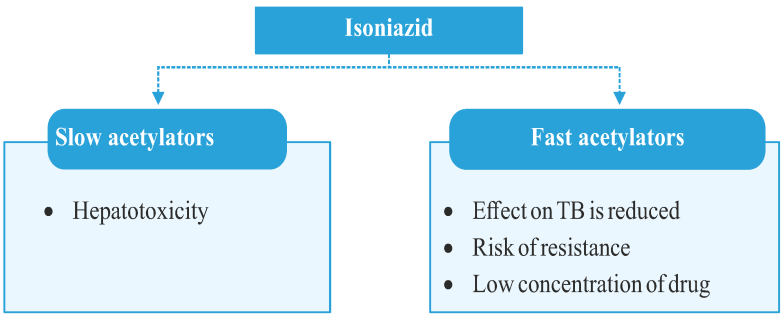
01:12:30

- In the liver, NAT (N-Acetyl Transferase) cause Acetylation
- Note: Mnemonic- SHIP-DP



- NAT also show genetic polymorphism





6 PHARMACOKINETICS: ELIMINATION

Elimination

00:00:05

- **Elimination**: Rate of removal of drug
- In absorption: The drug comes into the body with time
- In elimination: The drug present in the body gets removed from the body with time
- **Units:** mg/min
  - The amount of drug eliminated in certain timespan
  - Elimination rate
- Elimination include:
  - Site of elimination
    - → Known as excretion
    - → From where drugs get removed
  - Kinetics of elimination
    - → Speed at which drugs get removed
- **Elimination = Metabolism + Excretion**
  - Metabolise the drug into a water-soluble form
    - → The liver is most commonly involved in metabolism
  - Removing the drug through a route or pathway or site is called excretion
    - → Kidney is the most common site of excretion
    - → Most drugs get eliminated in urine

Excretion pathways

00:02:44

- Drug gets excreted out through body secretions
  - Urine
    - → Most drugs get removed through urine
    - → Major excretory pathway
  - Bile
  - Sweat
  - Saliva
  - Tears
  - Milk (lactating women)
  - Gases (exhaled through lungs)
- Drugs that are contraindicated during lactation due to their high excretory rate through milk; (Mnemonic: Small)
  - Sulfonamides
    - → Antibiotics
    - → Through milk, sulfonamides pass to the newborn
    - → Sulfonamides displace bilirubin from albumin
    - → Free bilirubin reaches brain of the neonate
    - → Lead to neuronal damage -kernicterus
  - Methotrexate
    - → Antifolate drug
    - → Reduces folic acid synthesis
  - Aspirin
    - → In newborns, this leads to liver damage
    - → Reye's syndrome
  - Lithium
  - Levetiracetam

PYQ

Q. Which drugs are excreted by sweat, saliva, and tears?

Ans. Lithium and metals like mercury

Q. Which antiepileptic drug gets excreted in the greatest amount in breast milk?

Ans. Levetiracetam

Gases

- Drugs excreted in gases:
  - Anesthetic gases
    - → Isoflurane
    - → Sevoflurane
    - → Halothane
  - 5 Fluorouracil
    - → Excreted as CO_2 and alcohols
    - → Alcohols converted to acetone
    - → Acetone excreted as gaseous form

Bile

- Not the major excretory pathway
- Reason:
  - If a drug is excreted in bile
    - → It can again get reabsorbed from the intestine
    - → With the help of intestinal bacteria
    - → Enterohepatic reabsorption
- **Example:**
  - Estrogen gets excreted through bile
    - → Conjugated by glucuronide
    - → Makes it water soluble
  - When it comes to the intestine
    - → Intestinal bacteria produce glucuronidase enzyme
    - → Enzyme removes glucuronide group from estrogen
    - → Estrogen becomes lipid-soluble
    - → Gets reabsorbed
    - → Returns to the liver
  - If antibiotics (doxycycline, ampicillin) are given
    - → Kills intestinal bacteria
    - → Inhibits enterohepatic reabsorption of estrogen
    - → Estrogen gets excreted out in feces
    - → Blood level of estrogen falls - estrogen is an oral contraceptive
    - → Antibiotics lead to contraceptive failure

PYQ

Q. Why does rifampin cause contraceptive failure?

Ans. Rifampicin increases the metabolism or degradation of estrogen by inducing CYP enzymes

Urinary excretion of a drug 00:12:33

- Urine is the major excretory pathway
- Most drugs get excreted in urine

Methods by which a drug enter into the urine.

1. **Glomerular filtration**
   - First method by which drug enters into urine

2. **ATS**
   - Active tubular secretion
     - Active process
     - Requires ATP
     - ATP acquired by specialized transporters
       - → Pick the drug from the blood
       - → Excrete out in urine
   - Drug enters the tubules of the nephron

3. **Passive reabsorption**
   - If the drug entered into urine has lipid solubility
   - Drug again gets reabsorbed into the blood
     - Not get excreted in the urine

Net urinary clearance (NUC)

- Net amount of drug that comes out in the urine

  Net urinary clearance = Glomerular filtration + Active tubular secretion - Passive reabsorption
- Normal GFR: 125 ml/min
- NUC > GFR
  - Here, active tubular secretion is also a dominant factor
- NUC < GFR
  - Drug is also getting passively reabsorbed
  - Passive reabsorption is a dominant factor
- NUC = GFR
  - No reabsorption
  - No secretion occur

Glomerular filtration

- Only the free form of the drug is excreted
- From the glomerulus, the drug enters the Bowman's capsule of the Nephron
- Capillaries of glomerulus contain endothelial cells
- Bowman's capsule contains podocytes
  - Have negative charge on them
- In filtration,
  - Drug passes through spaces between endothelial cells of glomerulus and podocytes of Bowman's capsule
  - Called paracellular spaces (pores)

- Filtration is a passive process
  - No ATP is required
- Predominantly acidic drugs (H^+) are filtered more
  - Compared to basic drugs (OH^-)
  - Podocytes carry a negative charge
  - Negative charge repel basic drugs
  - So acidic drugs are filtered more
- Plasma protein binding of a drug
  - Reduce filtration
  - Low Glomerular filtration in protein-bound drugs

Active tubular secretion

- Arteries run in parallel to renal tubules
- Transporters are present on renal tubules
  - Picks the drug from blood in arteries
  - Forcefully excreted in urine

- Active process
  - ATP is required
- Both free-form and protein-bound drugs can be excreted
- Transporters in the nephron helps in active tubular secretion
  - **OATP**
    - → Organic anion transport protein
    - → Excretes acidic drugs
    - → E g., antibiotics like penicillin and cephalosporins
  - **OCTP**
    - → Organic cation transport protein
    - → Excretes basic drugs
    - → E.g., Tubocurare (muscle relaxant)
  - **P-glycoprotein**
    - → Excretes neutral drugs
    - → E.g., Digoxin

Important Information

- When a free form of a drug gets excreted into the urine, the protein-bound drug, to maintain equilibrium, gets converted to free-form
- This free form gets excreted

PYQ

Q. What is the drug that inhibits the OATP transporter?

Ans. Probenecid

- Probenecid is combined with cephalosporins and penicillin because:
  - Probenecid inhibits the excretion of penicillin and cephalosporins into the urine
  - They remain in the blood for a longer duration
  - Makes them longer acting by inhibiting the excretion

Passive reabsorption

- Only water-soluble drugs get excreted in urine
- If the drug is lipid soluble (non-ionic) - gets reabsorbed back into the body

- In case of poisoning
  - Drug should be removed through urine
  - Make the drug more water-soluble
    → Inhibit Passive reabsorption

Example

- In case of weak acidic drug poisoning
  - Change the pH of urine
  - For treatment: Make the urine alkaline
    → Forced Alkaline Diuresis
  - Acidic drugs in basic urine becomes water-soluble
  - Drug used: Sodium bicarbonate
  - Weak acidic poisonings:
    → Aspirin poisoning
    → Acetaminophen poisoning
    → Barbiturates poisoning
    → Methotrexate poisoning

- In case of weak basic drug poisoning
  - Change the pH of urine to acidic
    → Forced Acidic Diuresis
  - Basic drugs in acidic urine becomes water-soluble
  - Drug used: Ammonium chloride
  - Basic drugs; (plant alkaloid)
    → Amphetamine poisoning
    → Strychnine poisoning
    → Morphine
    → Atropine
    → Quinine
- Drug can be changed to water-soluble only with weak acid and weak base
  - Urine pH is changed to promote excretion only in weak acid and weak base
- Strong acid and strong base
  - Not influenced by pH
  - Strong acids/bases always remain water soluble

PYQ

Q. What drug is used to make urine acidic in the basic drug poisoning?
Ans. Ammonium chloride

Q. What is an antidote for amphetamine poisoning?
Ans. Ammonium chloride

Important Information

- Amphetamine abusers mix it with sodium bicarbonate
  - Sodium bicarbonate makes urine more basic
  - Amphetamine (basic drug) in basic urine becomes lipid soluble
  - More reabsorbed
  - Increased level in blood
  - More pleasure from amphetamine

Kinetics of elimination

00:37:11

- Kinetics - by what speed does the drug get excreted out in urine

Clearance capacity [Cl]

- The power/capacity of an organ to eliminate a drug
- If the drug is administered, it gets absorbed into the blood
- The amount of drug present in plasma
  - Concentration of drug
  - Units - mg/ml
- When the drug reaches the kidney
  - Kidney excretes the drug into the urine
- The drug found in urine with time
  - Elimination rate: The amount of the drug getting out of the body in a given span of time
  - Units - mg/min
- Elimination (E) directly proportional to concentration ©)
  - More amount of drug present in plasma then more drug enters urine
- If an organ has high capacity or power
  - More drugs eliminated in urine
  - Elimination (E) directly proportional to Clearance capacity (Cl)

Important Information

Only for first-order kinetics,

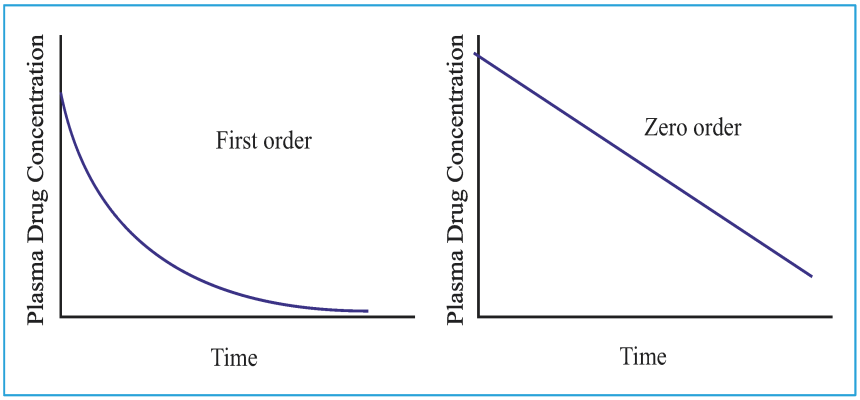
- Elimination = Clearance × Concentration of drug in plasma

- Units of clearance capacity: ml/min
- Clearance capacity: The volume of plasma (ml) that is cleared of a drug in a unit time (min)
  - Or the capacity/power of an organ to eliminate a drug
- Good clearance capacity
  - Drug follows the First order of kinetics of elimination
  - Excretion is fast
- Low/saturated clearance capacity
  - Drug follows Zero order kinetics of elimination
  - Excretion is slow

Order of kinetics of elimination

- 2 types
  - First-order kinetics
    - → Clearance capacity is very high (constant)
  - Zero order kinetics
    - → Clearance capacity is low (saturable)
    - → Also known as saturation kinetics
- In first-order kinetics
  - If the dose is increased, then more amount is excreted in urine
  - Plasma Concentration directly proportional to elimination
- Zero order kinetics
  - Increase in concentration does not change the amount of excretion of the drug
  - Elimination is constant and independent of plasma concentration

First order kinetics	Zero-order kinetics
Elimination directly proportional to plasma concentration	Elimination is constant Independent of plasma concentration
$T_{1/2}$ is constant	$T_{1/2}$ is directly proportional to plasma concentration
A constant fraction of the drug gets eliminated in unit time	A constant amount of the drug gets eliminated
Most drugs undergo first-order kinetics.	Very few drugs undergo zero-order kinetics.
Concentration-time graph of first-order kinetics show • Exponential decrease in plasma concentration	The concentration-time graph of zero-order kinetics show • Linear decrease in plasma concentration



Concentration-time graphs of first-order and zero-order kinetics

Examples of drugs that show zero-order kinetics at therapeutic dose

- Mnemonic: WHATSAP
  - W - Warfarin
  - H - Heparin
  - A - Alcohols
  - T - Theophylline
  - S - Salicylate
  - A - Aspirin (high dose)
  - P - Phenytoin

- All drugs
  - In low doses - First-order kinetics
  - In high doses - Zero order kinetics

- Example: Phenytoin
  - Shows first-order kinetics at low dose
  - At high doses shows zero order kinetics
  - At the Therapeutic dose(very high dose), it follows Zero order kinetics
- Exception: Alcohols
  - Only shows Pure zero-order kinetics at all doses

Pseudo-zero order kinetics

- In first-order kinetics -clearance capacity is not saturated
- In zero-order kinetics-clearance capacity is completely saturated
- If clearance capacity gets saturated gradually- Pseudo-zero order kinetics
- Phenytoin at therapeutic dose
  - Show both zero order kinetics + pseudo-zero order kinetics

7 PHARMACOKINETICS: HALF-LIFE, LOADING DOSE & MAINTENANCE DOSE

Formulas in PK

00:00:05

- ADME study

Absorption	Distribution	Metabolism & Excretion (Elimination)
1. BA[F] (Bioavailability) = $\frac{AUC(oral)}{AUC(i/v)}$ BA = $\frac{dose\ (i/v)}{dose\ (oral)}$ • i/v routes have 100% BA • Oral routes require a higher dosage • Area under curve- AUC	2. Vd = $\frac{Dose(i/v)}{plasma\ conc.}$ Vd = $\frac{dose\ (oral)\times F}{plasma\ conc.}$ • The volume of distribution - Vd • Dose (i/v) AKA loading dose (i/v) 4. Loading dose = Vd × Plasma concentration	3. Elimination = Clearance x Concentration (1st order kinetics) 5. Maintenance Dose MD = Clearance x Plasma concentration
	6. Half-life ($t_{1/2}$) = (0.693 x Vd)/Clearance	

Half-life ($t\frac{1}{2}$)

00:06:00

- Time required to reduce the plasma concentration of a drug by 50% after the drug has been completely absorbed

PYQ: NEET PG 2023

- Half-life of a drug does not depend upon:
  - Absorption → Half-life does not depend upon the route of administration
- Formula = Half-life ($t\frac{1}{2}$) = $0.693\ \frac{Vd}{CL}$

Important Information

- Half-life is calculated from the second phase of the distribution
- A drug has a high Vd → More drug enters the plasma → More drug remains in the plasma for a longer period → The drug takes a longer time to reach half of its initial concentration

$$t\frac{1}{2} \propto vD$$

- If the clearance capacity is good: Drug will be removed from the body faster

$$t\frac{1}{2} \propto \frac{1}{CL}$$

Important Information

Why use 0.693 (log 2)?

There is a pattern of decrease in plasma concentration

100

↓ $1t\frac{1}{2}$

50

↓ $2t\frac{1}{2}$

25

$\downarrow 3t\frac{1}{2}$

12.5

- Exponential decrease in plasma concentration.

Half-life $(t\frac{1}{2}) = 0.693 \frac{Vd}{CL} \Rightarrow (t\frac{1}{2}) = \frac{0.693}{K}$

$K = \frac{CL}{Vd}$ = Elimination Rate Constant

Half-life

$t\frac{1}{2}$	Plasma concentration	Elimination
0	100%	0%
1st	50%	50%
2nd	25%	75%
3rd	12.5%	87.5%
4th	6.25%	93.75%
5th	3.125%	96.875%

Q. In how many half-lives is 90% of the drug eliminated?
Ans. 3 - 4 $t\frac{1}{2}$

Q. In how many half-lives is 95% of the drug eliminated?
Ans. 4 - 5 $t\frac{1}{2}$

Q. In how many half-lives is 100% of the drug eliminated?
Ans. Never (∞).

- Everything must have a half value.

↓

- **Assumption in pharmacokinetics**
  - If a drug is eliminated more than 95% (plasma conc. < 5%) - We assume complete elimination of the drug
  - Complete elimination occurs in 4 to 5 $t\frac{1}{2}$

Q. If a patient takes lithium for many months and stops today, how many days will the action of lithium end?

Lithium: $t\frac{1}{2} \rightarrow 1$ day

Ans. Action will end after around 5 days of stopping lithium.

Exception: Hit-and-run drugs

Hit-and-run drugs 00:23:23

- Drugs which continues to produce action in the body even after complete elimination from blood/ plasma
- They bind to the target organs irreversibly (covalent bonds)
- Not present in plasma
- Also known as suicide inhibitors
- **Examples (Mnemonic: MOOGRA)**
  - MAO inhibitors (tranylcypromine)
  - Omeprazole (all PPI) → Inhibit H^+K^+ATPase irreversibly
  - Organophosphate
  - Guanethidine
  - Reserpine
  - Aspirin
    - → Inhibit cycloxygenase irreversibly
    - → Binds to platelet and inhibits cycloxygenase irreversibly
    - → Antiplatelet effect: 7 days
    - → Should be stopped 7 days before major surgery

Plateau Principle 00:30:15

- Also known as the steady-state concentration (Css) principle or target concentration
- If a drug is given by constant rate - It's 95% concentration in plasma is achieved in 4 to 5 $t_{\frac{1}{2}}$
  - Beyond this there is no significant increase in plasma concentration because:

Rate of infusion = Rate of elimination.

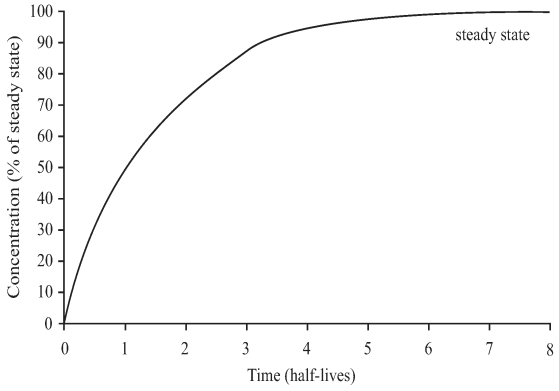


Figure 1: Concentration-time profile for a drug given by a constant rate infusion

Q. In case of an emergency, can you wait 4 to 5 days for the drug to exist in a patient's system?
Ans. No.

- Initially: A high dose (loading dose) is given to achieve Css rapidly.
- To maintain it: Drug is given externally to counter the drug eliminated inside the body (maintenance dose) to achieve the target concentration level

Target concentration level strategy

00:40:25

Loading Dose	Maintenance Dose
• Initial dose • Higher dose to achieve Css rapidly LD (i/v) = Vd x Target conc. Units: LD(i/v) = MG • Does not depend upon time • Does not depend upon $t\frac{1}{2}$ of a drug • Given for high Vd (volume of distribution) drugs	• Dosing rate • Given after a steady state is achieved MD (i/v) = CL x Target conc. ⇕ Elimination = CL x Target conc. Units: MD (i/v) = MG/min • Depend upon time • Depend upon $t\frac{1}{2}$ of a drug • Given for high-clearance drugs

Dose in renal failure

- Clearance capacity reduces → Reduce the maintenance dose of a drug
- No need to modify the loading dose

Dose in old age (Geriatrics)

- Reduced clearance capacity (decrease in GFR with age) → Reduce maintenance dose
  - Aminoglycosides require dose reduction in old age patients

Dose in children

- Best method to calculate dosing for children → Body surface area using the Dubois formula

  or

- Calculate the child's dose from the adult dose
  1. Young's formula

     $$\text{Child dose} = \text{Adult dose} \times \frac{\text{age}}{\text{age} + 12}$$

  2. Clarke formula
  3. Dilling formula

8 PHARMACODYNAMICS: AGONIST AND ANTAGONIST

- Pharma - drug; Dynamics - Effect produced by the drug
- The drugs produce their effect by binding to the target which can be a receptor, transporter, or enzyme.
- A ligand is any molecule (drug) that binds to the target and produces an effect.

Ligand and Its Types

- A ligand is a molecule having a high affinity for its target.
- It is also highly specific for its target.

Types of Ligand

Based on its nature

Endogenous ligands
- These are produced inside the body.
- E.g. Hormones, neurotransmitters

Exogenous ligands
- Ligands that come from outside into the body.
- E.g. Drugs, Poisons

Based on Intrinsic activity
- Agonist
- Antagonist

Agonist

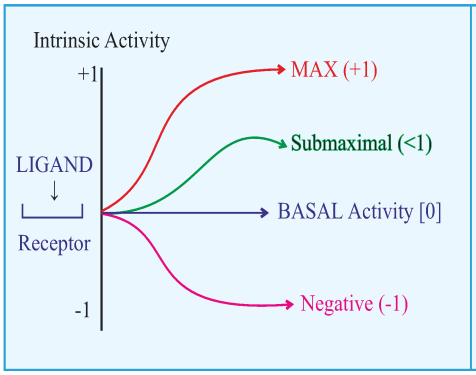
00:06:15

- These are the substances that produce effects.

Based on the quantity of effect
- Full agonist: Maximum effect, +1 IA
- Partial agonist: Low effect, 0 to 1 IA
- Inverse agonist: Negative effect, -1 IA

Example:

- Four drug molecules (ligands) namely A, B, C, and D act on β receptors of the heart
- Maximum heart rate (physiologically) = 200 bpm
- Basal heart rate = 70 bpm



- **Ligand A -** maximum effect (200 bpm), also known as Full agonist
- **Ligand B -** partial effect (150 bpm), also known as partial agonist
- **Ligand C -** zero effect (70 bpm), also known as an antagonist (neutral drugs).
- **Ligand D -** Negative effect (50 bpm), also known as Inverse agonist.

- Antagonists are also called neutral drugs since they produce no effect or "zero effect".
- Super-agonist- A drug leads to supra maximal response, > +1 IA
  - E.g. GnRH agonist drugs- Histrelin, Leuprolide

Effect Produced due to the Combination of Various Agonists and Antagonists

- Full agonist + high dose partial agonist = Acts as Antagonist (Decreases the effect from maximal towards basal line)
- Inverse agonist + High dose antagonist = Increases the effect from minimal to basal

Inverse Agonist 00:16:40

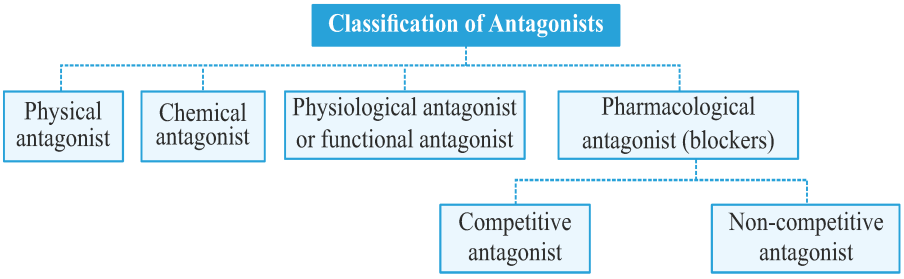
- Some receptors have basal activity, these receptors are continuously working and are called constitutive receptors.
- Inverse agonists act only upon constitutive receptors reducing their effect.
- Inverse agonists don't act on receptors that are not working continuously.

Example

Inverse agonist	Receptor	Response
β carboline	GABA-A	Increases seizure activity
Tiprolisant (Pitolisant)	Histamine (H_3)	In narcolepsy to prevent sleepiness
Rimonabant	Cannabinoid (CB1)	Decreases appetite

Antagonist 00:21:47

- A substance that inhibits the action of agonists.



Physical Antagonist 00:24:20

- Directly binds to the agonist surface by a physical bond and consequently reduces the movement of the agonist.
- **E.g.** Activated charcoal (antagonist) binds to the absorbed poison in the stomach

Chemical Antagonist 00:26:55

- Directly binds to the agonists by a chemical bond
- Acid vs base reaction i.e., neutralisation reaction occurs between agonist and antagonist.
- **Example**
  - Protamine sulfate (basic drug) acts as an antidote to HMW Heparin (acidic drug)
  - Antacids (neutralizes Hcl)
  - Chelators (used in metal poisoning)
  - Antibody (bind to the antigens)
  - Sugammadex (used as an antidote) neutralises muscle relaxants such as Vecurorium, rocuronium

Physiological Antagonist 00:30:10

- Physiological antagonists bind to different receptors to produce opposite effects, unlike agonists.
- **Example**
  - Histamine acts on H_1 receptors and causes bronchoconstriction
  - Adrenaline acts on β_2 receptors leading to bronchodilation

Agonist	Physiological antagonist	Inverse agonist
Agonist	Physiological antagonist	Inverse agonist
↓	↓	↓
Same target	Different target	Same target
↓	↓	↓
Same effect	Opposite effect	Opposite effect

Examples of Agonist vs Physiological Antagonist

Agonist	Physiological antagonist
Histamine- Bronchoconstriction	Adrenaline- Bronchodilation
Leukotrienes- Bronchoconstriction (LT receptor)	Salbutamol- Bronchodilation (β_2 receptor)
PG-I_2- Antiplatelet action	Thromboxane- Platelet aggregation
PTH- Hypercalcemia	Calcitonin- Hypocalcemia
Insulin- Hypoglycemia	Glucagon- Hyperglycemia
β-blocker- Decreases heart rate	Glucagon- Increases heart rate

Important Information

- Antidote for β-blocker poisoning is Glucagon.

Pharmacological Antagonist 00:37:05

- Also known as Blockers.
- Blocks the target of the agonist.
- **E.g.** Adrenaline (agonist) binds to α or β receptors
  - α-blockers - Phenoxybenzamine
  - β-blockers- Propranolol
- Classified based on how they block the receptors

Competitive antagonist	Non-Competitive antagonist
Competitive antagonist is similar in structure to agonist	Non competitive antagonist structure is different compared to agonist
↓	↓
Competes with the agonist	Binds to allosteric site
↓	↓
Binds to the same target as agonist	Modifies the structure of the target
↓	↓
Blocks the agonist from binding to the target	Reduces the affinity of agonist to its target
↓	
Zero activity	

- **Competitive antagonist vs non-competitive antagonist**

Competitive antagonist	Non-competitive antagonist
Same target binding	Allosteric site binding
Similar in structure to agonist	Different structure
Surmountable effect: An increased dose of agonist overcomes the effect of a competitive antagonist	Non-surmountable effect: Cannot overcome the effect of non-competitive antagonist
Affinity to target: Reversible binding>>>Irreversible binding	Affinity to target: Irreversible binding >>>reversible binding

Irreversible competitive antagonists

- Competitive antagonists are also called uncompetitive blockers when they irreversibly bind to the target, and the effect produced is "unsurmountable".

Examples

Competitive + Irreversible blocker (Uncompetitive blocker)	Non-competitive + Reversible blocker

• Methotrexate inhibits DHFR enzyme
  ○ DHFR(Dihydrofolate reductase) converts folic acid to tetrahydrofolate.
  ○ Methotrexate competitively and irreversibly inhibits DHFR
• Organophosphate inhibits the Cholinesterase enzyme
	• Acetazolamide inhibits carbonic anhydrase

Q. Is the structure of methotrexate like folic acid? True or false?

A. True

Q. Can we overcome the effect of methotrexate by folic acid? True or false?

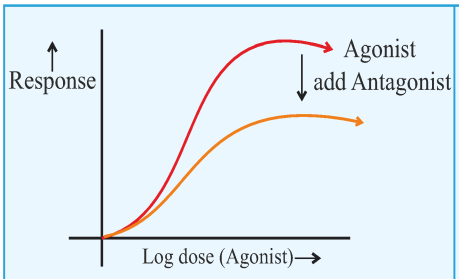
A. False

Important Information

- Antidote for methotrexate poisoning is Folinic acid (Tetrahydrofolate)

Dose-Response Curve

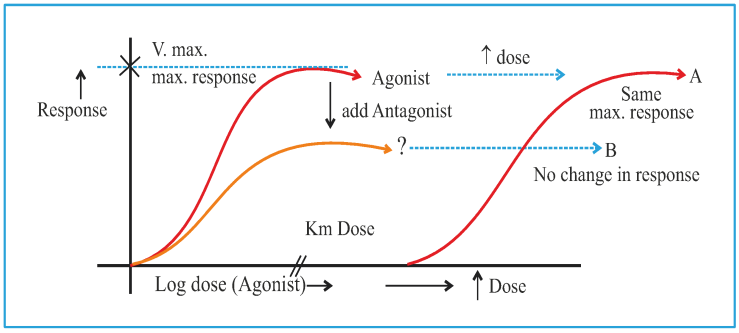
00:55:20



- When an antagonist is added, the agonist response is decreased (represented by an orange line)

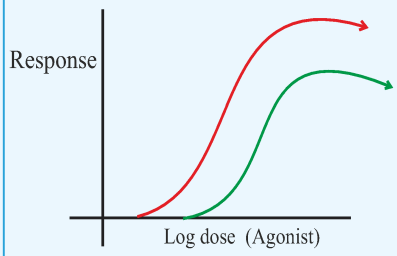
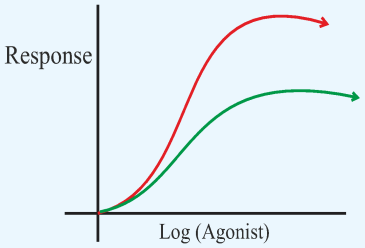
How to find out whether the antagonist is competitive or non-competitive?

- Increase the dose of agonist



- In the first case (A) the same level of response is produced.
- In the second case(B), there is no change in response
- It is therefore concluded that
  - A is a Competitive antagonist since it shows a surmountable effect
  - B is a Non-competitive antagonist since it doesn't show a surmountable effect.
- V_{max} is the maximum response produced by the drug
- K_m is the dose at which the maximum response is produced.

Competitive Antagonist vs Non-Competitive Antagonist based on DRC 00:59:20

Parameter	Competitive antagonist	Non-competitive antagonist
Graph		
Shift in graph	Rightward parallel shift in DRC	Reduction in height/ slope of DRC
V_{max}	No change (constant)	Decreased
K_m	Increased	No change (constant)

Michaelis Menten constant 01:03:00

- V_{max} and K_m are known as the Michaelis Menten constant used in the dose-response curve.
- The shape of the dose-response curve is sigmoid.

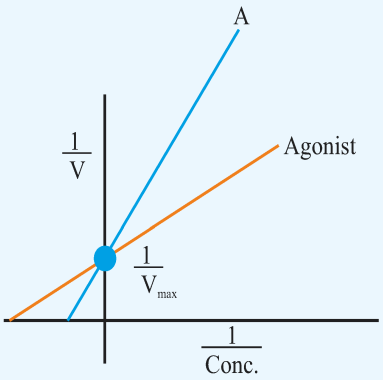
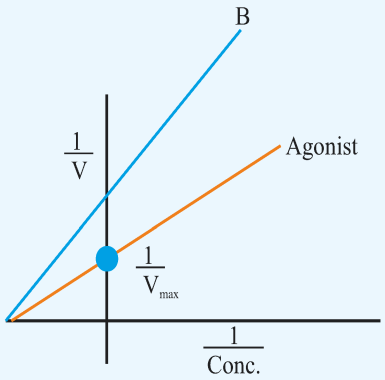
$$V = \frac{Vmax \times Concentration\ of\ agonist}{Km + Concentration\ of\ agonist}$$

- Double reciprocal of the equation gives -

$$\frac{1}{V} = [\frac{Km}{Vmax}] \times \frac{1}{Concentration\ of\ agonist} + [\frac{1}{Vmax}]$$

- This straight-line plot of Michaelis Menten equation is known as Lineweaver Burk plot

Effect of Competitive and Non-Competitive Antagonists on Lineweaver Burk Plot.

Competitive antagonist	Non-competitive antagonist
• V_{max} = Constant • K_m = Increased	• V_{max} = Decreased • K_m = Constant
	

9 PHARMACODYNAMICS: DOSE RESPONSE CURVE

- Dose of the drug vs response
- **Other name:** Concentration effect curve
- **Two types :**
  - On the basis of dose
  - On the basis of response

Dose-Response Curve based on Dose

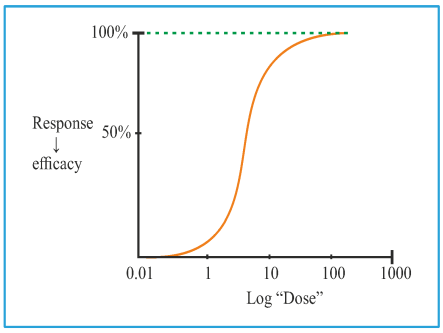
00:01:12

1. Normal DRC

- Most drugs produce a sudden response
- Slight increase in dose produces a significant response
- **Shape of the curve:** Parabola
- Not very useful

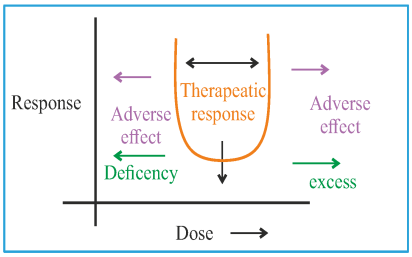
2. Log DRC

- Mostly used in pharmacology
- **Shape of the curve:** Sigmoid
- We can compare different doses with different responses



3. U-Shaped DRC (Rare)

- **1st part:** Less dose gives adverse effect (deficiency)
- **2nd part:** Therapeutic response (optimum dose)
- **3rd part:** High dose gives adverse effect (excess)
- **Example:** Vitamins, minerals, and hormones



Important Information

Example

- Insulin
  - Less - Diabetes
  - Excess - Hypoglycemia
- Iron
  - Less - Anemia
  - Excess - Hemochromatosis
- Vit-A
  - Less - Night blindness
  - Excess - Liver and other organ damage

Dose-Response Curve on the basis of Response.

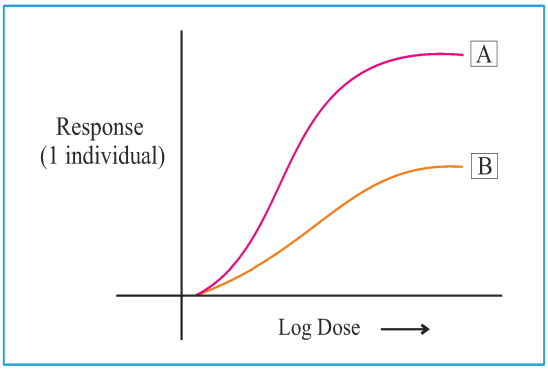
00:06:40

1. **Graded DRC**
   - If the dose is increased gradually, the response also increases
   - **Example:** Antihypertensives
   - Determination of response in 1 individual
   - Used to find out:
     - Efficacy
     - Potency

2. **Quantal DRC**
   - If the dose is increased - all or none response
   - **Example:** Antiepileptic (completely suppress seizures or not at all), antiemetic
   - Determination of response in a population (%)
   - Find out
     - Effective dose
     - Toxic/lethal dose
     - Therapeutic index

Graded DRC

00:11:11



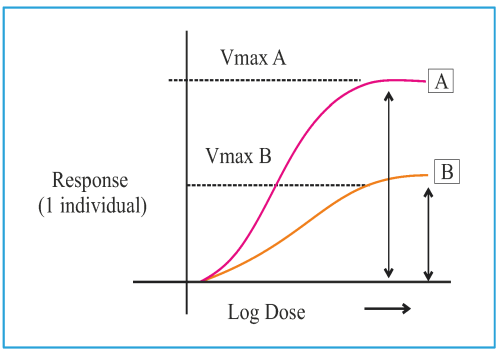
Log dose-response curve of individual

PYQ: FMGE 2020, 2023

- Drug A produces a high response
- Drug B produces less response

Efficacy

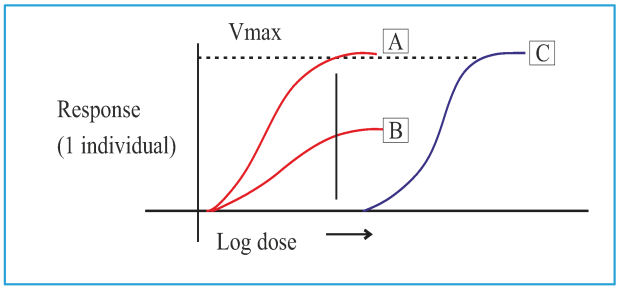
- Maximum response produced by the drug
- (Does not depend on dose)
- **Symbol:** Vmax



Graph of efficacy

PYQ: FMGE 2021

- Here, A has more efficacy than B
- Height/ slope is more - Efficacy is more



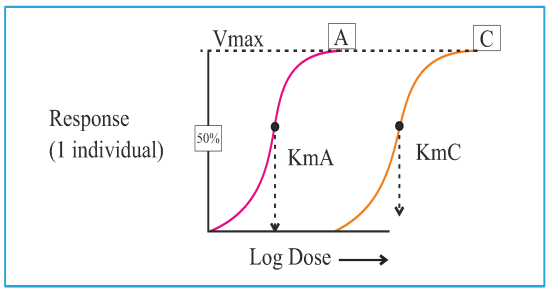
Graph with 3 drugs

- Efficacy of A and C have the same level of Vmax (maximum response)
- A = C > B
- C requires more dose, but A needs less dose

Potency (Km)

- Dose required to produce 50% of max response
- Depends on dose
- **Symbol:** Vmax/2

PYQ: INICET 2019

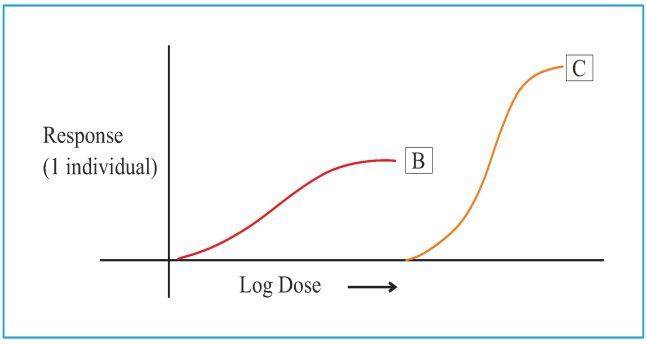


Graph of potency

- Km of A is less
- Km of C is high
- Determined on the basis of left sidedness
- Less dose means more potent
- Here, A is more potent

Important Information

- More height is more efficacy
- More left-sided, more potent



Drug B vs. C graph

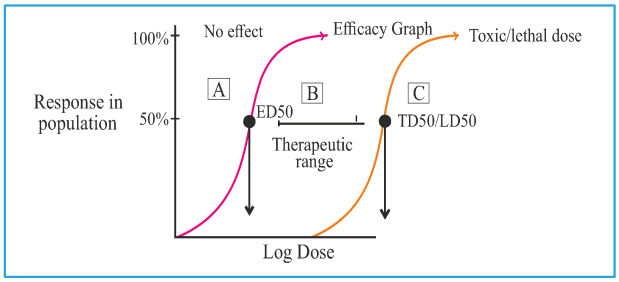
- **Efficacy:** C > B
- **Potency:** B > C

- Choice of a drug depends upon efficacy
- If the efficacy of two drugs is equal, drug with more potency is preferred
- Vmax and Km are Michaelis Menten constants

Quantal DRC

00:21:47

- % of population



Quantal DRC

Effective Dose

- Dose for beneficial response
- ED50
  - **Other name:** Median effective dose
  - Dose that produces a therapeutic effect in 50% of the population

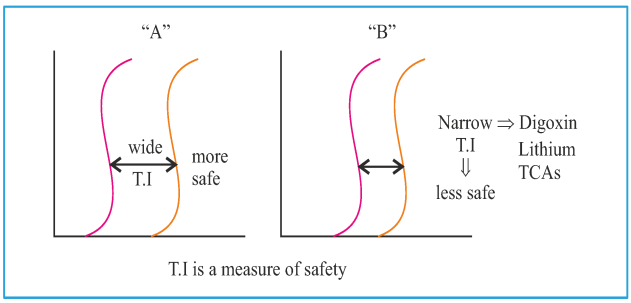
Toxic Dose/ Lethal Dose

- **Other name:** Median toxic/lethal dose
- After a certain level, the drug becomes harmful
- TD50/LD50
  - Dose that produces toxic or lethal effects in 50% of the population

Therapeutic Range

- Area A - No effect of drug
- Area B - Therapeutic effect
- Area C - Toxic effect
- Range of ED50 to TD50 is called Therapeutic range
- **Example**
  - The therapeutic range of Phenytoin in blood is 10-20 mcg/ml
    → <10 : not effective
    → >20 : toxic
- **Therapeutic Range Values**
  - **Phenytoin:** 10-20 mcg/ml
  - **Valproate:** 50-100 mcg/ml
  - **Phenobarbitone:** 15-40 mcg/ml
  - **Digoxin:** 0.6-2.0 ng/ml
  - **Theophylline:** 5-15 mcg/ml
  - **Lithium:** 0.5-1.5 meq/ml
  - **Vancomycin:** 5-15 mcg/ml

Therapeutic Index



- TD50/ED50 or LD50/ED50
- **TD50 - humans**
- **LD50 - animals**
- If the ratio is very small, i.e., ED50 and TD50 values are close to each other
  - Slight increase in dose can lead to toxicity
- Therapeutic index: safety margin of drug
  - If T1 value is small
    - → Drug is unsafe
    - → Narrow Therapeutic index drugs
    - → Monitoring is required
  - If T1 value is large - Safe to use

Monitoring of Narrow Therapeutic Index Drugs

00:36:50

- **Monitoring toxic effect**
  - Example: a slight increase in Insulin dose can lead to hypoglycemia (monitor blood glucose)
  - Clonidine (monitor BP)
  - Warfarin (monitor PT)
  - Heparin (monitor aPTT)
- **Monitoring plasma concentration**
  - Done for drugs for which toxic effects cannot be monitored
    - → Lithium changes mood
    - → Phenytoin
    - → Cyclosporine
  - Other name: TDM (Therapeutic Drug Monitoring)

Important Information

- TDM is costly, hence done only for some cases
- So monitoring toxic effects for the possible drugs is preferred

Drugs Requiring Therapeutic Drug Monitoring

00:41:41

- **Mnemonic:** DAAT, LAAT, CC

• **D**igoxin • **A**minoglycosides (Gentamicin, Streptomycin) • **A**ntiepileptic drugs • **T**heophylline	• **L**ithium • **A**ntiarrhythmics • **A**ntipsychotics • **T**ricyclic antidepressants	• **C**alcineurin inhibitors (Cyclosporine, Tacrolimus) • **C**ancer drugs (Example - Methotrexate)

Important Information

- SSRIs do not require TDM, thus DOC for depression
- All anticancer drugs need TDM
- TDM is most commonly done in Cyclosporine and Tacrolimus

Do vs. Not to do TDM (Therapeutic Drug Monitoring)

00:44:42

Do TDM	Don't Do TDM

• Must do in case of narrow Therapeutic index drugs (low safety margin)
• Cannot monitor the toxic effects
  ○ Lithium
• Poisoning of drug
• Nephrotoxic drugs in renal disease
  ○ Aminoglycosides
• To check the compliance (timely intake of drugs)
  ○ Antiepileptics (Phenytoin) - If missed, can cause rebound seizures
	• Wide safety margin
	• Can easily monitor the toxic effects
	  ○ Insulin
	  ○ Warfarin
	• Hit and run drugs
	  ○ Irreversibly attached to organs
	  ○ Not present in plasma
	  ○ Ex: Aspirin
	• Pro-drugs
	  ○ Converted into another metabolite

10 PHARMACODYNAMICS: DRUG RECEPTORS

Drug Targets

1. **Protein targets:**
   - Receptors
   - Ion-channel (voltage-gated ion channel)
     - Lignocaine blocks Na^+ voltage-gated ion channel
   - Carriers (transporters)
     - Loop and thiazide diuretics
   - Enzymes
     - Acetazolamide, Atorvastatin

2. **Antacid:** Neutralizes Hcl
   Chelators: Binds to circulating metals

Receptors

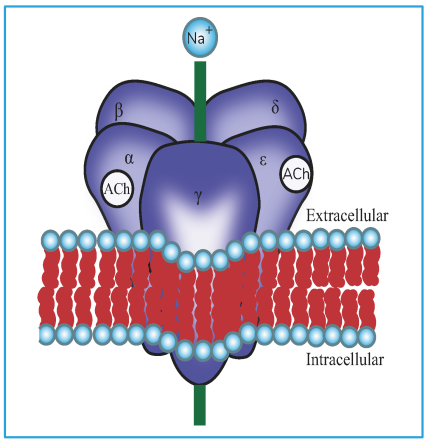
00:03:00

- 4 types of receptors in a cell:
  - 3 of these types are present on the cell membrane
    1. Inotropic receptor
    2. G protein-coupled receptor
    3. Enzyme-linked receptors
  - 4th receptor is present inside the cell → Intracellular receptor (nuclear receptor)

1. Inotropic receptor

00:04:55

- Also known as ligand-gated ion channel
- Structure
  - Pentameric rosette with 5 subunits (α, β, γ, δ and ε)
  - α & β are mandatory



- Function
  - Ligand binds to α - β junction - Opens the inotropic receptor.
  - This leads to an ion influx of sodium and chloride
    → Na^+ : Depolarize = Excitatory
    → Cl^- : Hyperpolarization = Inhibitory
- Fastest-acting receptor (<1 msec)
- They do not require a second messenger

Important Information

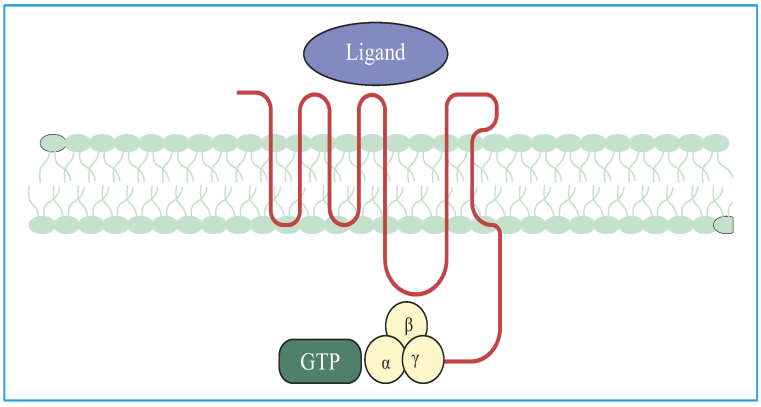
Q. What are the examples of inotropic receptors?

1. Na^+: Excitatory
   - Nicotic receptor (acetylcholine)
   - $5HT_3$ receptor (serotonin)
   - NMDA receptor (glutamate)
2. Cl^-: Inhibitory
   - GABA-A Cl^- Channel
   - Glycine-Cl^- Channel

2. G protein-coupled receptor (GPCR)

00:13:30

- Most important receptor
- Metabotropic receptors → Requires 2nd messenger
- Structure: Snake-like receptor coupled with a G protein
  - Receptor is 7 transmembrane helical (serpentine shape)
  - G protein is an α, β and γ hetero trimer
    → α subunit contains the GTP molecule



- Function
  - Ligand binds to receptor → Activation of G protein
    → α subunit separates from β and γ
    → α has enzymatic activity → Phosphorylation of enzymes
    → α subunit = Active subunit of the G protein which will produce an effect inside the cell

Q. How does the α subunit of the G protein produce an effect within cells?

Types of G protein		
Gs	**Gq**	**Gi**
Activates adenylyl cyclase • Converts ATP into cAMP • Increase the level of cAMP • cAMP starts the protein kinase A (PKA) pathway	**Activates phospholipase C** • Breaks down phospholipids • Increases the level of IP_3 (inositol triphosphate) and DAG (di-acyl glycerol) • DAG starts PKC pathway • IP_3 will travel to smooth endoplasmic reticulum and release calcium. This calcium (3rd messenger) will start a calmodulin pathway.	**Inhibits adenylyl cyclase** • Reduces the level of cAMP • Opens potassium channel - Leads to potassium efflux. • Leads to hyperpolarization of cell

- **2nd messengers**
  - cAMP
  - IP3
  - DAG
- Gs & Gq → Excitatory
- Gi → Inhibitory

List of 2nd messenger and pathway (signal transduction)

1. cAMP: Protein kinase A pathway
2. IP3: Calcium calmodulin pathway
3. DAG: Protein kinase C pathway
4. cGMP: Protein kinase G pathway

Nitric oxide gas

- Activates guanylyl cyclase
  - This soluble guanylyl cyclase floats around in the cytoplasm
  - Converts GTP into cGMP
  - cGMP → PKG pathway
- Nitric oxide gas is produced inside blood vessels via endothelial cells
- Goes to smooth muscles of blood vessels: Increases cGMP and causes vasodilation
- Nitric oxide is also known as endothelial-derived relaxing factor (EDRF): Causes smooth muscle relaxation and blood vessel dilation

  cAMP ⟶ 5' AMP

  cGMP ⟶ 5' GMP
- Enzyme that deactivates the effect of cAMP and cGMP: Phosphodiesterase (PDE)
- PDE inhibitors increase the level of cAMP and cGMP
- Sildenafil
  - Increases cGMP → Vasodilation
  - Given for the treatment of erectile dysfunction/ impotence

Important Information

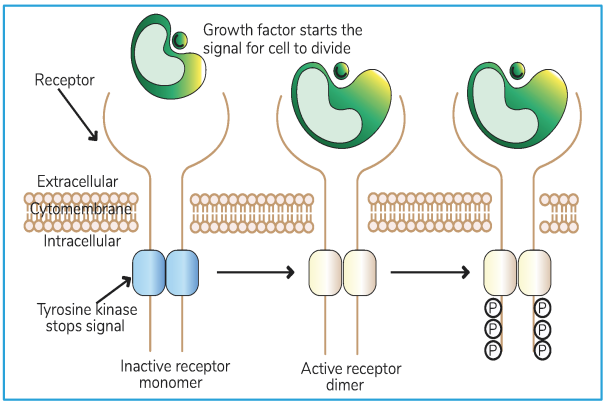
Examples of molecules that act on GPCR (largest family of receptors)

- Muscarinic receptors (acetylcholine)
- $5HT_1$ to $5HT_7$ (except $5HT_3$)
- α and β (epinephrine and norepinephrine)
- All hypothalamic receptors
- All pituitary hormones (except growth hormones and prolactin)
- Pancreatic hormones like somatostatin (Gi) and glucagon (Gq) (except insulin)
- Photoreceptors (retina) - Gt
- Odorant receptors (olfactory nerves) - Go

3. Enzyme-linked receptors

00:41:52

- Protein kinase receptors
- Also known as growth receptors → Increases cell division
- Structure
  - Receptor (protein) + Enzyme (kinase)



- Function
  - 2 ligand molecules binds to the receptor - Causes the receptor to fuse
    - → Auto-phosphorylation of a kinase enzyme
    - → Mitogen-activated protein (MAP) kinase pathway

↓

Cell division (mitosis)

Types of kinase enzymes

- Tyrosine kinase receptors → Insulin
  - IGFR (insulin-like growth factor receptor)
  - VEGFR (vascular endothelial GFR)
  - EGFR (epidermal GFR)
  - PDGFR (platelet-derived GFR)
- Serine/threonine kinase
  - TGFR (transforming GFR)
- JAK-STAT receptor
  - JAK: Janus kinase (just another tyrosine kinase)
  - STAT: Signal transduction & activation of transcription
  - E.g.
    - → Growth hormone
    - → Prolactin
    - → Erythropoietin
    - → Thrombopoietin
    - → Interleukin / Interferon

} Cytokine Receptors

PYQ.

Q. What molecule controls our appetite in the brain and acts on the JAK-STAT receptor?

Ans. Leptin

Q. If there is a DNA mutation occurring inside the cell and there is a gain of function (excessive action) - What is the result?

Ans. Uncontrolled cell division = Leads to cancer (Lung cancer: Mutation inEGFR)

Q. What are protein kinase inhibitor drugs used for?

Ans. Anti-cancer drugs (end with -nib)

E.g.

Drug	Blocks	Used for
Imatinib	BCR-ABL	CML tumor
Erlotinib	EGFR	Lung cancer
Sunitinib	VEGFR	Renal cell carcinoma

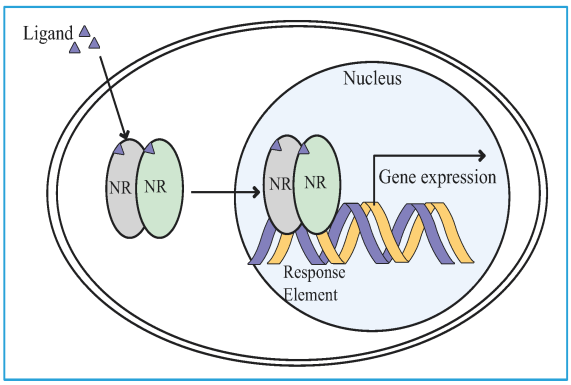
4. Intracellular receptors

00:59:45

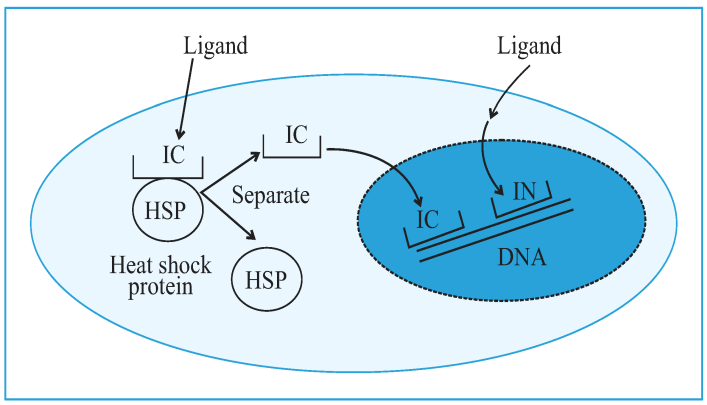
- Found inside the cell or the cytoplasm (intracytoplasmic)
- Also known as nuclear receptors
  - Act through DNA
  - Increase gene transcription: Coactivator
  - Decrease gene transcription: Corepressor
- Slowest receptors
- Sustained effect

Based on location

1. **Intranuclear receptor** → Already inside the nucleus
   - **T** - Thyroid receptors (T_3/ T_4)
   - **A** - Vitamin A(retinoic acid receptor)
   - **P** - PPAR (Peroxisomal Proliferator Activating Receptor)
   - **E** - Estrogen receptor



2. **Intracytoplasmic receptor** → Translocate to the nucleus after ligand binding
   - Attached to heat shock protein (HSP) when not working
   - HSP prevents the entry of intracytoplasmic receptors into the nucleus
   - When ligand attaches to the intracytoplasmic receptor - It separates from HSP
   - Intracytoplasmic receptors then enter the nucleus
   - Steroidal hormones
     - Glucocorticoid receptors (cortisol)
     - Mineralocorticoid receptor (aldosterone)
     - Androgen receptor (testosterone)
     - Progesterone receptors
   - Calcitriol receptor → Vitamin D_3



Properties of Receptors

01:12:00

1. **Promiscuity of ligand**
   - 1 ligand binds itself to multiple receptors
     - E.g.:
       → Acetylcholine: Nicotinic receptor - Ionotropic receptor
       → Acetylcholine: Muscarinic receptor - GPCR
2. **Spare receptor**
   - Extra receptors or more than required receptors

PYQ.

- EC_{50}: Concentration of ligands to produce an effect
- KD_{50}: Concentration of ligands to occupy all receptors
- Spare receptors: KD_{50} - Ec_{50}

3. **Desensitization of receptors**
   - Reduced activity of a receptor on prolonged agonist exposure
     - Leads to loss of effect
   - Development of tolerance
   - Mechanism:
     1. Internalization and degradation of receptors
     2. Reduced signal transduction
     3. Arrest in binding

Q. Why does FSH/LH value reduce on prolonged/ continuous action of GnRH agonist?
Ans. Desensitization of GnRH receptors on pituitary

4. **Supersentivity of receptors**
   - Exaggerated receptor response - Due to prolonged antagonist exposure
   - Mechanism:
     1. Increase in density of receptor
     2. Increase in signal transduction

Q. What is the reason for never stopping β blockers suddenly on your patient?
Ans. β receptors on SA node have become supersensitive and will result in rebound tachycardia/ hypertension

11 DRUG DEVELOPMENT AND CLINICAL TRIALS

Steps in drug development

Drug discovery

↓

Animal and lab testing
(pre-clinical trials)

↓

Human testing
(clinical trial)

↓

Marketing of drug

IND application
- After the preclinical trial, IND application is submitted to proceed with clinical trials
  - IND - Investigational New Drug application
- In America, IND submitted to FDA-USA
- In India, IND is submitted to CDSCO (Central Drug Standard and Control Organisation)

NDA application
- After clinical trials, to obtain market approval for the drug NDA application is submitted
  - NDA - New Drug Application
  - To FDA - In America
  - To CDSCO - In India
- After NDA approval, the drug can be marketed and prescribed

Drug discovery

00:04:22

Sources of drugs

Nature

Plants
- Morphine from the poppy plant (Papaver somniferum)
- Atropine from datura plant

Animals
- Monoclonal antibodies
- Vaccines

Microorganisms
- Penicillin G from fungus Penicillium notatum
- Streptomycin from bacteria Streptomyces

High throughput screening
- It is a method of screening all available chemicals
- Most common method of finding new potential drug

Rational drug designing
- New drugs made according to target receptors to which the drug binds
- Example: Proton pump inhibitor - Omeprazole

- The chemical that has the potential to become a drug is called HIT
- Pre-clinical trials are done on HIT/potential drug

Preclinical trial

00:08:16

- A preclinical trial is animal and lab testing of a drug
- **Purpose**
  - To evaluate the safety and efficacy of a drug
- To evaluate the safety of drugs, toxicity studies are conducted
  - The drug is administered in different doses at different time intervals to the animals and they are studied for any organ damage.

Single-dose toxicity study	Multiple dose toxicity study

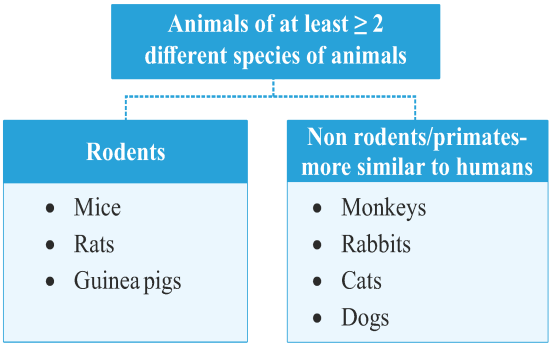
• Single dose administered
• To evaluate if the drug has acute toxicity (within 1 day)
	• Multiple doses given to animals
	• To evaluate:
	  ○ Subacute toxicity: 1 week to 1 month
	  ○ Chronic toxicity: >6 months

- Following toxicity studies, the animal is killed and its organs are checked for toxicity like Nephrotoxic, Hepatotoxic, Neurotoxic, Genotoxic or Carcinogenic to ensure the safety of the drug

Guidelines for preclinical trial

- GLP guidelines (Good Laboratory Practices guidelines)
  - Explains about how to perform preclinical and lab testing

Animals taken in preclinical trial



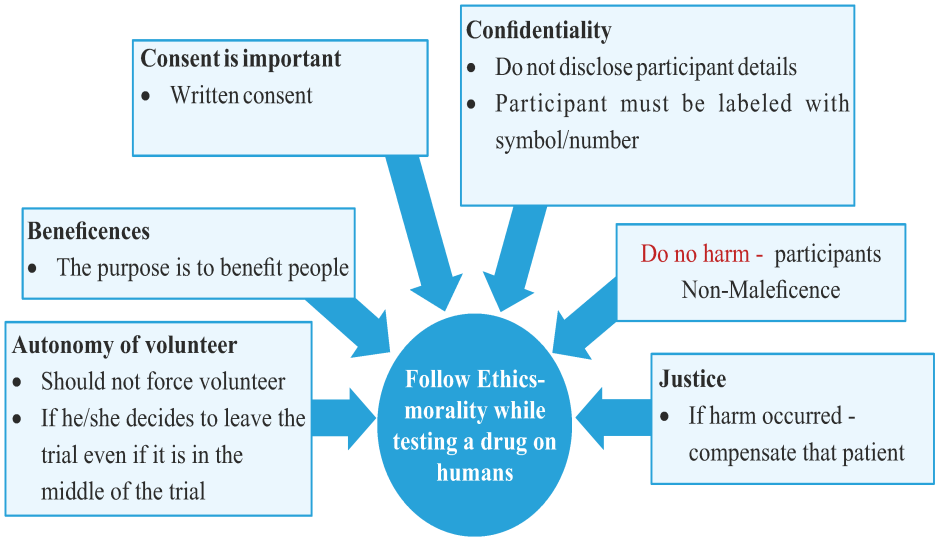
- Rodent species are most commonly used as they are easily handled and easy to store in animal house
- Ideal weights of species
  - Mouse - 20-40 grams
  - Rats - 40-80 grams
  - Guinea pigs - 150-200 grams
  - Rabbits - 1.5 to 1.8 kgs
- Ideals weights are equivalent to a human of 60 kg
  - Dose in animals is converted to human equivalent dose and used in clinical trials

- **Example**
  - In a preclinical trial of the drug Thalidomide
  - Drug was tested only on rats which was found to be safe but showed teratogenic activity in humans

Clinical trials

00:16:20

- Clinical trials is human testing of a drug
- Guidelines followed in human testing
  - GLP guidelines: Good Laboratory Practice
  - GCP guidelines: Good Clinical Practice
- GCP guidelines



Ethical guidelines followed globally: ICH-GCP

- International Council on Harmonization - Good Clinical Practices
- In India, ICH-GCP guidelines are a law
  - Enforcing the guidelines and punishment or fining if not followed
- Indian law: NDCTR - 2019
  - New drugs and clinical trial rules

Phases of clinical trials

00:23:00

- Clinical trials are done in phases
- All 4 phases are mandatory to get the drug approved
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4
- Non-mandatory phase
  - Phase 0: Done before Phase 1
- After phase 3: The drug gets market approval

Phase 0 clinical trial

- Also known as micro-dosing trial
- Non-mandatory clinical trial
- Very low dose is given (subtherapeutic dose) - 100 micrograms dose
  - Dose is attached to radiolabeled isotope/radio-isotope
  - Drug circulates in the body and the radioactivity is detected on a PET scan
- If the drug is not binding to its target, phase 0 trial is avoided as it is expensive.

Number of volunteers	Type of volunteers	Design of trial	Purpose
2-5	Healthy humans	Open-label (no blinding) - the person is aware of the trial	• Target binding of a drug • Pharmacokinetics of the drug

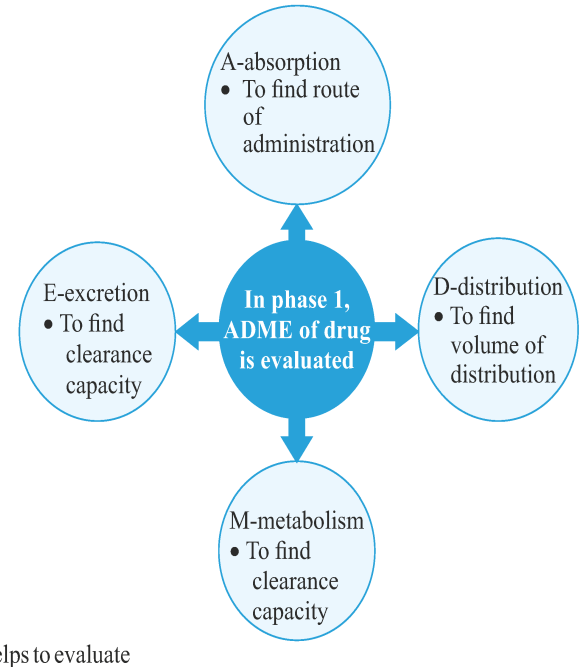
Phase 1 clinical trial 00:29:50

- Mandatory phase
- Also known as the first in human trial
  - As drugs first time enter into human body
- Known as human safety and pharmacology trial
- The dose calculated by testing on animals is administered in humans (human equivalent dose)
- As phase 1 is first in humans, evaluating safety is more important

Number of volunteers	Type of volunteers	Design of trial	Purpose
20-50	Healthy humans	Open-label trial (no blinding)	1. To evaluate the safety of the drug 2. To evaluate MTD 3. Pharmacokinetics (ADME) of drug

Evaluation of drug safety

- If 50 humans are taken
  - Divided into groups of 5 or 6
- In one group, a 20 mg dose is given, to the next group 30 mg dose and in the next group 40 mg dose
  - After 40 mg, the drug starts producing toxicity
  - So, above 40 mg that drug is harmful
  - This safety limit is called the maximum tolerable dose/MTD



  - ADME helps to evaluate
    - → Half-life of drug
    - → Loading dose
    - → Maintenance dose

Q. Phase 1 trial is not done for?

Ans. Phase 1 is not done to evaluate the efficacy of the drug

- To evaluate efficacy, the drugs must be tested on patients
- Phase 1 is done on healthy humans, so efficacy can not be evaluated

Q. Phase 1 trial is mainly done for?

Ans. Phase 1 trial is mainly done to evaluate the maximum tolerable dose of the drug

- Because safety is done in all phases of clinical trials

Phase 2 clinical trial 00:36:40

- Known as Therapeutic Exploratory Trial

Number of volunteers	Type of volunteers	Design of trial	Purpose
200-500	Patients	• RCT - randomized clinical trial • RCT+Single blinding-the patient is unaware of the actual drug	Explore efficacy- By finding dose range at which the drug is effective – hence called proof of concept trial

Exploratory efficacy

- The dose of the drug does not exceed the maximum tolerable dose.
- For example;
  - MTD - 40 mg
  - In one set of people, 10 mg given
  - In another set 20 mg and 30 mg in another
  - The drug was found to be effective at a dose range of 20-40 mg
  - Explore efficacy by finding the dose range

Phase 3 clinical trial 00:40:15

- To find one single dose from the dose range
  - The drug is tested on a large number of patients
  - Done in phase 3 clinical trials
- Known as Therapeutic Confirmatory Trial

Number of volunteers	Type of volunteers	Design of trial	Purpose
2000-5000 (Thousands of people)	Patients	RCT + blinding (double blinding) - both the patient and prescribing doctor are unaware	Confirm efficacy- Confirm the actual dose of the drug

- Phase 3 is also known as the Multi-site trial as it is conducted at different places simultaneously since it is difficult to find a large no. of patients with similar diseases in one place
- Done on a heterogeneous population
- Safety is priority: Any side effect that is not seen in Phase 1 may be seen in Phase 3 as the drugs get exposed to a large number of people
- After phase 3 clinical trials, the actual dose is confirmed and the drugs get market approval

Phase 4 clinical trial 00:44:44

- After marketing, drugs get prescribed to a large population
- The missed or hidden side effects in phases 1,2 and 3 may be seen after marketing

- So drug safety is monitored even after market approval which is the phase 4 clinical trial
- Known as post-marketing surveillance

Number of volunteers	Type of volunteers	Design of trial	Purpose
Cannot be predicted	Patients taking an approved drug	Open-label (no blinding)	• Evaluate safety- To find hidden/missed/rare adverse effects that were missed in phase 1,2 and 3 trials • Compliance: long-term side effects • Drug interactions • Food interactions

- In phase 4, if a drug is found to be more harmful/toxic
  - The drug should be withdrawn from the market/banned

Q. What is the minimum duration of the phase 4 trial for marketed drugs?
Ans. ≥ 2 years

- It is mandatory to continue the phase 4 trial at least 2 years after approval
- If the drug is harmful, phase 4 time will be extended

Overall summary of phases of clinical trials

The phase of clinical trial	Number of volunteers	Type of volunteers	Design of trial	Purpose
Phase 0	2-5	Healthy people	Open-label	• To identify target binding • To check the pharmacokinetics of the drug
Phase 1	20-50	Healthy people	Open-label	• To evaluate safety • To calculate MTD • Pharmacokinetic parameters (Not for efficacy)
Phase 2	200-500	Patient	RCT + blinding	• Explore efficacy
Phase 3	2000-5000	Patient	RCT + blinding	• Confirm efficacy - find the actual dose of the drug
Phase 4	Unpredictable	Patient	Open-label	• Rare or missed adverse effects

Q. After which phase of the clinical trial, does the drug get approval for marketing?
Ans. Phase 3 clinical trial

Q. Which phase of clinical trials is done on approved drugs?
Ans. Phase 4 trial

Q. Among phases 1, 2, and 3, Which phase of clinical trials has the maximum sample size?
Ans. Phase 3 clinical trial

Q. Among phases 1, 2, and 3, Which phase of clinical trials is called a Multi-site trial?
Ans. Phase 3 clinical trial

Q. Among phases 1, 2, and 3, Which phase of clinical trials is done on heterogeneous populations?
Ans. Phase 3 clinical trial

Q. Among phases 1, 2, and 3, Which phase of clinical trials gives the best data on the safety of a drug?
Ans. Phase 3 clinical trial
- Best safety data in Phase 3 > Phase 2 > Phase 1

Q. Among phases 1, 2, and 3, Which phase of clinical trials has the best data on efficacy?
Ans. Phase 3 clinical trial
- Phase 3 > Phase 2 in efficacy
- Efficacy is not found in phase 1 clinical trials

Q. Among phases 1, 2, and 3, Which phase of clinical trials is the most costly?
Ans. Phase 3 clinical trial – due to maximum sample size

Q. Among phases 1, 2, and 3, Which phase of clinical trials have maximum failure rates?
Ans. Phase 2 clinical trials
- Efficacy is first found in phase 2 – more chances of failure

Q. Among phases 1, 2, and 3, Which phase of clinical trials did RCT with/without blinding?
Ans. Phase 3 and Phase 2 clinical trial

Bridging trials

00:55:58

- Bridging the gap between two different countries
- Only phase 3 is done to get approval for drugs in one country which has already been approved in another country

Hypothetical case scenario
- Drug A got approved in Europe
- If Drug A needs to get approved in India or another country
  - Only have to do the phase 3 clinical trial
  - This trial is called the bridging trial

Efficacy Vs Effectiveness

00:57:55

Efficacy	Effectiveness

• Beneficial effect of a drug in a controlled environment
• In Phase 2 and Phase 3, efficacy is evaluated
  ○ Under controlled environment
  → Specific dose
  → At specific times
  → Specific food intake by participants
	• Beneficial effect of the drug in a real-world environment
	• In phase 4 clinical trial, effectiveness is evaluated
	  ○ People take drugs at their home
	  ○ No control
	  → Take medicine at different times
	  → No restrictions on food intake

α and β error

00:59:40

- During clinical trials in humans, false results (error) may be obtained
  - False results/error is not an actual result

α error	• If a drug is not effective in reality but clinical trials have shown it as effective • The trial is giving a false positive result
β error	• If a drug is effective in reality but clinical trials have shown it as not effective drug • The trial is giving a false negative result

- Errors are reduced by RCT + blinding
- Bias is a kind of false result- Reduced by blinding

Important Information

- If the patient is unaware - single blinding
- If the patient and doctor, are both unaware - double-blinding

12 TYPES OF DRUGS, ADVERSE DRUG REACTION AND PHARMACOGENETICS

Types of drugs

1. Placebo

00:00:05

- Also known as dummy drug
- Actual drug contains active moiety and excipients
  - Active moiety: Produces some effect on the body
  - Excipients:
    - → Color of the drug
    - → Buffer capability to maintain pH
    - → And of various types
- Placebo drug is exactly similar to actual drug
  - Do not contain active moiety
  - Contains inert substance with excipients
  - So, color taste is similar to the actual drug
- **Use:** Randomised controlled trials
  - In one group, the actual drug is given
  - Placebo is given to another group to compare the effect
  - Placebo is used as comparator
- By giving a placebo, the patient can have psychological improvement
- **Example:**
  - Chloroquine is tested in two groups
  - To check its action on headache
  - To one group, the actual drug is given
  - To another placebo is given
    - → Instead of actual effect
    - → There is psychological improvement
  - Compare the effect
    - → Whether the effect produced by the actual drug, in reality, is actual or not
- Placebo helps in blinding
- Single blinding
  - Patients are unaware of placebo and actual drugs
- Double blinding:
  - Both doctor and patient are unaware of placebo
- Blinding helps to remove bias (false results) in a study

Sham surgery

- In a clinical trial to find the effectiveness of surgery
  - Fake surgeries are done called sham surgery

- It's a counterpart for placebo
- **Example,** two groups of patients, A and B:
  - In group A, if a patient comes with abdominal pain
    - → An abdomen incision is done to remove the appendix
    - → Then assess whether the abdominal pain is reduced or not
  - In group B, for abdominal pain, the same abdominal incision done
    - → But the appendix is not removed
    - → Assess whether the pain is reduced or not
  - This finds whether the appendectomy is beneficial or not

2. Orphan drugs

00:06:30

- Drugs used for very rare diseases
- Drugs for rare disease
  - In India; Rare disease - the prevalence of disease is <1 per 5 lakh population
  - In USA; Rare disease - the prevalence of disease is <1 per 2 lakh population
- In India, the government gives incentives/money to pharmaceutical companies to make orphan drugs
  - As they are rarely used, pharmaceutical companies generally do not make rare drugs

Rare disease	Orphan drug
Acute iron poisoning	Desferioxamine (iron chelator)
Digoxin poisoning	Digibind (antibody against digoxin)
• Methanol • Ethylene glycol poisoning	Fomepizole
Lennox Gastaut syndrome	Felbamate
SCID (severe combined immunodeficiency syndrome)	Adenosine deaminase enzyme (enzyme replacement)

3. Essential drugs

00:10:45

- Drugs used for highly prevalent diseases
- **WHO definition:** Drugs that satisfy the priority healthcare needs of the majority of the population.
- It is the responsibility of the government to keep essential drugs available
  - Available at all time
  - In all doses
    - → Doses for children
    - → Dose for elders
    - → Dose for special populations like pregnancy, renal disease, hepatic disease
  - In all types of formulations
    - → Tablets
    - → Injection
    - → Syrups
  - Affordable cost-effective
- The prices of essential drugs in India are controlled by the government
  - Regulatory body - NPPA
    - → National Pharmaceutical Pricing Authority

- Essential drugs must be available as a single medicine
  - Avoid combining with other drugs - combination drugs (FDC)
  - Combination drugs are costlier
- Every 2 years, WHO takes out essential drug list
  - 1st list of essential drugs made in 1977
  - The latest list came in 2023 - 23rd of essential drugs
  - Another list will be made in 2025
- According to WHO, 23rd list of essential drugs
  - For Adults: 502 drugs are essential
  - For Children: 361 drugs are essential
- In India, the essential drugs list is made by modifying the WHO list of essential drugs
  - India has separate essential drugs list
  - Because Indian healthcare needs are different from the world
- Essential drugs list of India: NLEM
  - National list of essential medicine
  - The latest list was in 2022, with 384 drugs

4. Fixed dose combination (FDC) 00:17:10

- Combination of two or more drugs in a single formulation
- Essential drugs are avoided as FDC
- FDC is done in two scenarios
  - Scientific reason (should combine two drugs)
    - → Rational FDC
  - Unscientific reasons (should not combine drugs)
    - → Irrational FDC
- **Rational FDC**
  - Synergism
    - → Additive (1+1=2) - the combined effect is similar
    - → Supradditive (1+1=3) : Cotrimoxazole
  - Side effects reduce
    - → One drug reduces the side effects of other
    - → Imipenem-highly nephrotoxic antibiotic combined with Cilastatin (reduces nephrotoxic effect)
  - Improve compliance
    - → In chronic diseases, multiple drugs are prescribed
      - – Leads to non-compliance
    - → FDC can improve compliance
    - → Example: metformin + glimepiride (FDC for Diabetes)
  - Reduce the risk of resistance
    - → Seen in antibiotics
    - → For TB; isoniazid + rifampicin + pyrazinamide + ethambutol as FDC.
    - → For HIV, 3 antiretroviral drugs are given as FDC
- **Irrational FDC**
  - Antagonism (1+1<2)
    - → Combined effect is less
    - → One drug is reducing the effect of another drug
    - → Should be avoided

- Side effects are increased
  - → Avoid the FDC
- Cost is increasing
  - → Most irrational FDCs are combined to increase the cost
  - → Government bans irrational FDC from time to time
- Different pharmacokinetics
  - → 2 hours and another
  - → Have two different dosing schedules
  - → FDC of these two drugs is irrational

5. Counterfeit drugs 00:23:50

- Illegal drugs
- Given with intention to cheat or harm a person
- People making illegal drugs are punished or jailed
- **Types**
  - Spurious drugs (falsified drugs)
  - Misbranded drugs (substandard drugs)
  - Adulterated drugs
- **Spurious drugs**
  - Have no active ingredient
  - Example, 500 mg paracetamol tablet
    - → When checked, contains no paracetamol in it
  - Done by illegal people other than the manufacturer
    - → To copy drug
- **Misbranded drugs**
  - Low-quality drugs
  - Example, 500 mg tablet
    - → Contain only 200 mg when checked
  - The same manufacturer makes misbranded tablets
    - → To increase profit
- **Adulterated drugs**
  - Addition of harmful or unwanted excipients
  - GMP guidelines do not approve these substances
    - → GMP: Good manufacturing practices
    - → Explains the safe list of chemicals that are added to a drug
  - Example
    - → In Africa, few children died due to cough syrup made in India
    - → That syrup contains ethylene glycol - a harmful alcohol
    - → Ethylene glycol is not approved as an excipient by GMP
    - → This is adulterated

Q. Who can open a chemist shop?

A. MBBS

B. MD/MS

C. B-pharmacy

Ans. B-pharmacy graduates

- Pharmacy students are specialized in storing the drugs, in dispensing it
- They obtain a license to open a chemist shop

6. Schedule drugs 00:29:00

- Schedule means laws that regulate a drug
- **Schedule H**
  - Known as prescription drugs
  - Not dispensed without a prescription
  - Carry R_x symbol
    - → Means 'take thou' in Latin
  - Even in OPD cards, the R_x symbol is made
- **Schedule X**
  - Narcotic/psychotropic drugs
  - Have addiction potential
    - → People abuse these drugs
  - Carry the NR_x symbol
    - → – narcotics
  - Chemists keep a copy of the prescription to dispense narcotics for at least 2 years
  - Examples:
    - → Ketamine
    - → Opioids - morphine
    - → Barbiturates
    - → Benzodiazepines - alprazolam
    - → Amphetamines

PYQ

Q. What is the general anesthetic Schedule X drug?

Ans. Ketamine

- **Schedule G**
  - Only given under medical supervision
    - → Given in front of a doctor or nurse
    - → Not taken home
  - Because they cause a lot of side effects
  - **Example:**
    - → Amphotericin B – antifungal drug
      - Cause a lot of allergy
      - Patient dies due to anaphylaxis
    - → Anti-cancer drugs
    - → Misoprostol - leads to abortion
- **Schedule Y**
  - Scrapped/removed by the law
  - Changed to NDCTR-2019

The expiry date of a drug 00:34:34

- Last day of the month mentioned in the label
- Expiry date importance is in legal implication
- After the expiry date, the drug is consumed, the manufacturer has no responsibility regarding quality
- Drug advertisement/ Drug promotion: Done by a Medical representative

- Drug label
- Indication of drug
- ADRs
- All data should be given except the expiry date

7. Teratogenic drugs

00:38:00

- Lead to fetal harm if used in pregnancy
- US-FDA category of teratogenic drugs, 5 categories
  - **A:** Safest in pregnancy
  - **A, B, C, D:** given in pregnancy
  - **X:** most dangerous
    - → Absolutely contraindicated in pregnancy

Category	Meaning	Example
A	Human fetus: safe	• Folic acid: commonly used in pregnancy • Doxylamine: vomiting in pregnancy
B	• In humans: studies are lacking • In animals: safe	Risk cannot be ruled out
C	• Human: studies are lacking • Animals: Teratogenic	Animal teratogenic
D	• Human teratogenic • Given in pregnancy ○ Benefit > teratogenic risk	Antiepileptic: Valproate • Teratogenicity: Neural tube defect • Sudden stoppage: Sudden seizures, death • Saves the life of the mother

X	• Human teratogenic
	  ○ Teratogenic risk > Benefit
	• Contraindicated in pregnancy
		• Thalidomide, control vomiting
		• Teratogenicity: Congenital malformation
		  ○ Phocomelia

- Teratogenic drugs: D, X

Drugs

- Mnemonic TERATO Causes Various MALformations
  - Thalidomide
    - → Category X
    - → Phocomelia in the fetus: Small limbs
  - Epilepsy drugs
    - → Category D
    - → Valproate: Neural tube defects (Spina bifida)
    - → Given to avoid seizures in pregnancy
  - Retinoic acid
    - → Vitamin
    - → Category X
    - → Causes various malformations
  - ACE inhibitors
    - → Category X

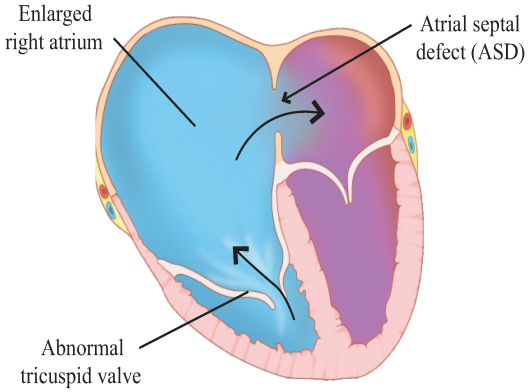
→ Enalapril, Lisinopril

→ Renal agenesis: Inhibit kidney formation in the fetus

- Tetracycline
  - → Category X
  - → Chelates with calcium in the fetus
  - → Reduce bone growth
    - Bone and cartilage defect
- Estrogen/Hormonal preparation
  - → Category X
  - → Change the gender of the fetus
- Carbimazole/Methimazole
  - → Antithyroid drugs
  - → Contraindicated in the first trimester
  - → Cause Aplasia cutis
    - No skin formation, especially in the head
- Warfarin
  - → Contraindicated in first trimester (12 weeks)
  - → Bone and cartilage defects
    - Saddle nose
- Methotrexate
  - → Antifolate drug
  - → Category X
  - → Neural tube defect
- Alcohol drinking
  - → Category X
  - → Fetal alcohol syndrome
- Lithium
  - → Category D
  - → Ebstein anomaly
    - – Heart defect

Phocomelia in a baby due to Thalidomide

Aplasia cutis due to Carbimazole/Methimazole



Ebstein anomaly due to lithium used in bipolar disorder

PYQ

Q. Which of the following is a Schedule X drug?

A. Thalidomide

B. Enalapril

C. Methotrexate

D. Ketamine

- Thalidomide, Enalapril and Methotrexate are Category X drugs
  - Teratogenic drugs
- Schedule X drugs are narcotic and psychotropic drugs
  - Addictive potential

8. Drug storage temperature

00:51:00

Freeze	-10 to -20°C
Cold	<5°C
Cool and dry	8-15°C
Warm	30-40°C
Excessive heat	>40°C

9. Drug compendia

00:52:00

- Compendia: Compilation of drugs available
  - Pharmacopeia
  - Formulary

Pharmacopoeia	Formulary
Based on chemical properties • Melting point • Boiling point • Excipients • Storage temperature	According to • Use • Dose • Adverse effects
Important for drug manufacturers	Healthcare professionals
• India: Indian Pharmacopoeia (IP) • Britain: British Pharmacopoeia (BP) • America: United States Pharmacopoeia (USP)	National Formulary of India (NFI)

Aspirin tablets

10. Nomenclature of a drug

00:56:11

a. Chemical name

- Given by IUPAC
  - International Union of Pure and Applied Chemistry
- E.g.: Acetyl Salicylic acid

b. Non-Proprietary name

- Can be used universally
- **AKA:** Generic name
- Given by INN (International Nonproprietary Nomenclature)
- In India, Doctors must prescribe in generic names only
- E.g.: Aspirin

c. Proprietary name

- Given by Manufacturers
  - Property of manufacturer
- Brand/Trade names
- E.g.:
  - Ecosprin: Cipla
  - Deplatt: Pfizer

11. Adverse Drug Reaction (ADR)

00:58:56

- Unwanted, Unintended (not expected), harmful effects of a drug
- Adverse event (AE) differs from ADR
  - AE is any harmful event that may or may not occur due to a drug
  - ADR is due to a drug
- Causality assessment is used to identify the relation of ADR to drug
  - Pharmacovigilance find out the reason for ADR and AE
- **Pharmacovigilance**
  - Pharma: Drug
  - Vigilance: To keep check on drug
  - Assess, monitor and report any ADR
  - Causality assessment: Question the patients, whether the AE or ADR is due to drug or not
    - → Rechallenge test: Event after re-administration of drug
    - → Dechallenge test: Stop drug
    - → Duration of AE onset
  - Methods in causality assessment
    - → Naranjo scale
    - → WHO-UMC scale

- ADR form
  - Filled by any healthcare professionals
  - Uploaded on computer on a software: Vigiflow
  - Send to National Pharmacovigilance Centre
    - → IPC (Indian Pharmacopoeia Commission), Ghaziabad, UP
      - – Very Harmful: Banned
      - – Little harmful: Reported as side effects
  - Global Pharmacovigilance center
    - → WHO-UMC (Uppsala Monitoring Center) center, Sweden

Naranjo scale

S. No.	Please answer the following questionnaire and give the pertinent score	Yes	No	Do not know	Score
1	Are there previous conclusive reports on this reaction?	1	0	0	
2	Did the adverse event occur after the suspected drug was administered?	2	-1	0	
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	0	
4	Did the adverse reaction reappear when the drug was readministered?	2	-1	0	
5	Are there alternative causes (other than the drug) that could have on their own caused the reaction?	-1	2	0	
6	Did the reaction reappear when a placebo was given?	-1	-1	0	
7	Was the blood detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0	
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	
10	Was the adverse event confirmed by any objective evidence?	1	0	0	
				Total	

Definite	If the overall score is 9 or greater
Probable	for a score of 5 -8
Possible	For 1-4
Doubtful	If the score is 0

Types of ADRs

Type of ADR	Example
A: Augmented dose • High dose • Toxicity • Prevented by reducing dose	High dose of insulin leads to Hypoglycemia.

B: Bizzare • Any dose • Allergic/Hypersensitive • Idiosyncratic • Nonpreventable • Genetically determined: Due to genetic make-up	Penicillin allergic reaction seen in 2:100 people
C: Chronic/continuous use • Reaction seen after chronic usage of drug	• Aspirin-induced peptic ulcer • PPIs taken for longer duration cause calcium deficiency • PPis lead to osteoporosis
D: Delayed onset • After stopping the drug, ADR appears after many years	Secondary cancer due to anti-cancer drug • Cisplatin administered and stopped in a cancer patient • After 3-5 years, another cancer develops.
E: End of treatment • Sudden stoppage of drug shows harmful reactions • Withdrawal reactions	Opioids' sudden stoppage leads to withdrawal reactions.
F: Failure of therapeutic effect • Drugs do not show a beneficial effect	TB drugs that do not kill TB bacteria • Antimicrobial resistance

12. Pharmacogenetics/Pharmacogenomics

01:14:50

- Pharma: Drug
- Genetics/Genomics: the genetic makeup of an individual
- Variation in drug response due to the genetic makeup of an individual
- Pharmacogenetics: Variation due to single gene
- Pharmacogenomics: Variation due to whole genome
  - Future of pharmacology

Drug	Pharmacogenomic Test
Warfarin	VKOR-C1 enzyme + CYP2C9 enzyme

Azathioprine/6-Mercaptopurine	TPMT (Thiopurine Methyltransferase) enzyme
	• Degrade thiopurines
	• In some individuals, the mutant variety does not degrade thiopurines
	  ○ Azathioprine toxicity:
	  → Bone marrow suppression
	• Widely available

5-Fluorouracil (Anticancer)	DHPD (dihydropyrimidine dehydrogenase) enzyme • Degrade 5-FU
Succinylcholine	Pseudocholinesterase degrades succinylcholine. • Dibucaine number

Irinotecan, Atazanavir	Degraded by UDP-GT A1 enzyme
	• Uridine Di-phosphate glucuronyl transferase
	• Attaches glucuronide and excretes drugs
	• Deficient in (Contraindicated)
	  ○ Crigler Najjar syndrome
	  ○ Gilbert syndrome

Abacavir (Anti HIV)	In HLA-B 5701-positive people, it causes allergic reactions • HLA genetic testing needed

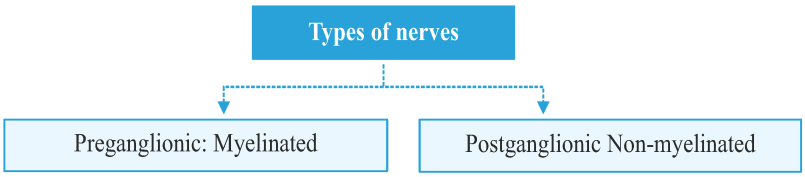
Important Information

Drugs avoided in G6PD deficiency

- Deficiency of antioxidant - Glutathione (Protects RBC)
- Damage of RBC → hemolysis
- Drugs avoided (Mnemonic: MAD FANS)
  - Metronidazole
  - Aspirin
  - Dapsone
  - Fluoroquinolone
  - Antimalarials
  - Drugs containing Nitro groups
    → Antihypertensive: Nitroprusside
    → Antibiotic: Nitrofurantoin
  - Drugs containing Sulfa groups
    → Sulfonamide
    → Anti TB: Isoniazid
  - Methylene blue (dye)
  - Fava beans (food products)
  - Chloramphenicol

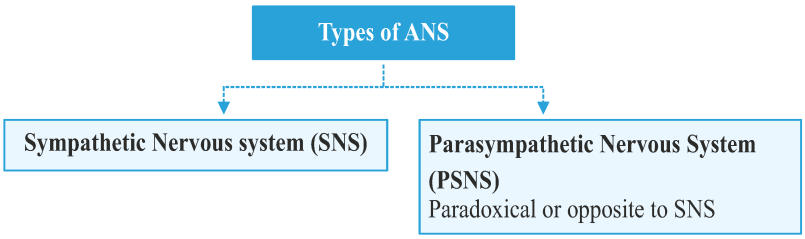
13 INTRODUCTION AND ACETYL CHOLINE

- The autonomic nervous system controls autonomous functions, also known as visceral functions.
  - Examples: Heartbeat, Blood pressure, Acid secretion in the stomach, Miosis and mydriasis



Classification of ANS

00:01:25



Sympathetic	Effect	Parasympathetic
• Functions in emergencies	**Conditions**	• Relaxed condition • Also known as the rest and digest system
• Increases	**Heart rate**	• Low
• Dilate	**Bronchus**	• Constriction
• Dilates- mydriasis	**Pupil**	• Miotic, constricts
• Relaxes bladder, reduced sense of urination	**Bladder**	• Constriction, increased urination
• Reduced acid secretion	**Stomach**	• Increased acid secretion
• Relaxed	**Intestine**	• Contraction, frequent defecation
• Lipolysis	**Adipose**	• Lipogenesis
• Ejaculation	**Penile**	• Erection

Relevant anatomy

00:06:33

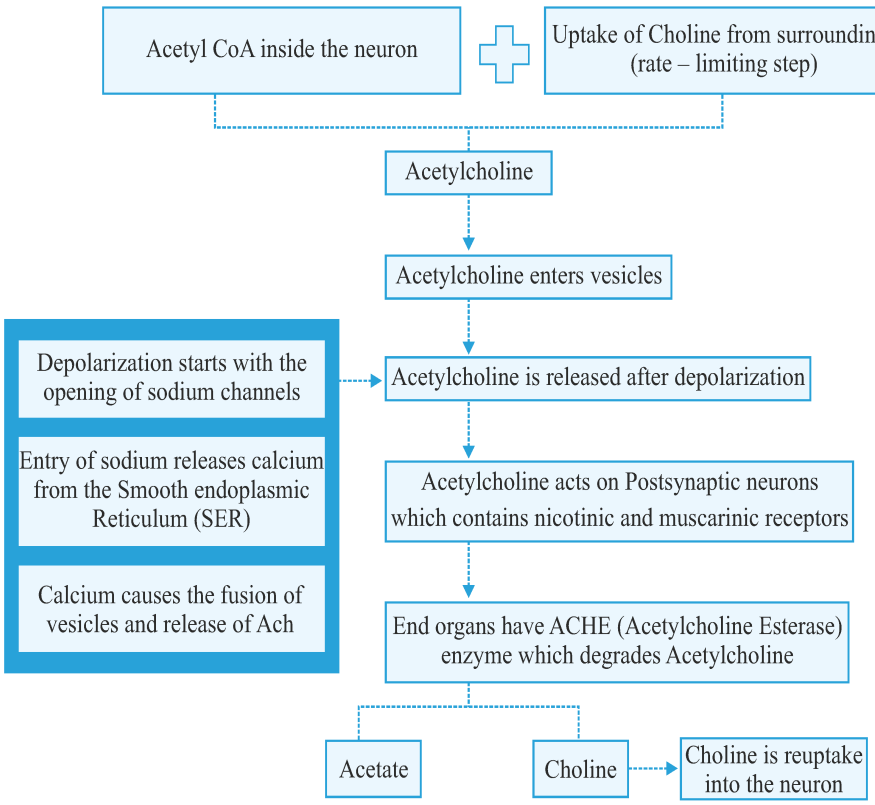
SNS	PNS
• Adrenergic Nervous system	• Cholinergic Nervous System
• Thoracolumbar outflow, T1-L2	• Cranio-Sacral outflow • 3,7,9,10 cranial nerves and S1-S4 carry the parasympathetic fibers.
• Small preganglionic nerve synapses with a long postganglionic nerve	• Long Preganglionic nerve synapses with the short postganglionic nerve

• Preganglionic neurotransmitter: Acetylcholine	• Preganglionic neurotransmitter: Acetylcholine
• Postganglionic receptor: N_N (Nicotinic neuronal) receptor	• Postganglionic receptor: Nn (Nicotinic neuronal) receptor
• Postganglionic neurotransmitter: • Norepinephrine: All sites (major) • Dopamine: kidney, GIT (minor)	• Postganglionic neurotransmitter: Acetylcholine
• Innervate Adrenal medulla: Releases Epinephrine into the blood	-
• End organ receptors: Alpha and Beta	• End organ receptors: M (muscarinic) receptor and Nicotinic
• Effect in SNS is produced by Catecholamines ○ Epinephrine/ Adrenaline ○ Norepinephrine / Nor-Adrenaline ○ Dopamine	• The effect is only produced by Acetylcholine only

- Certain post-ganglionic nerves also release Acetylcholine, these nerves are called sympathetic cholinergic nerves and they innervate end organs
  - Sweat glands- increase sweating
  - Blood vessels- vasodilation
  - These end organs have M (muscarinic) receptors

Acetylcholine

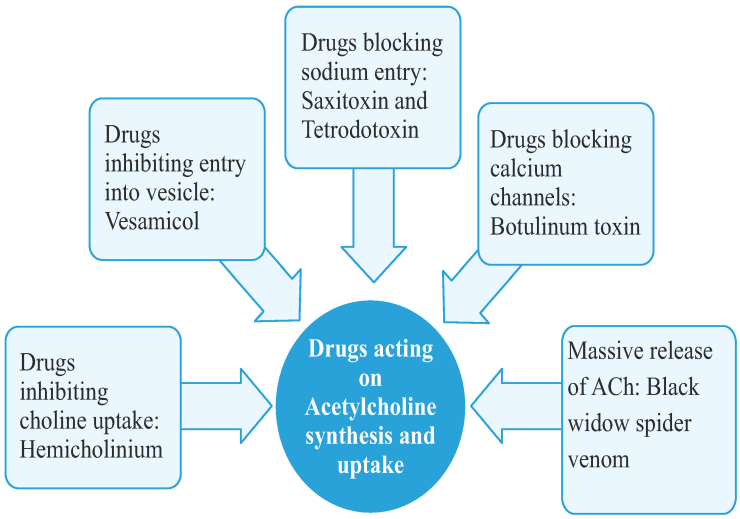
00:19:30



- Endogenous acetylcholine is released at the synapse and degraded by ACHE
- Exogenous acetylcholine from a drug enters blood plasma which is degraded by
  - BACHE (Butyrylcholinesterase) or PACHE (Pseudocholinesterase)

Important Information

- Anticholinesterase drugs inhibit ACHE/ PACHE
  - Carbamate
  - Organophosphate
- Inhibit degradation of acetylcholine
- Increases level of endogenous ACh and parasympathetic activity in our body



Botulinum toxin

00:30:00

Mechanism of action

- Inhibit the release of Ach from nerves by blocking calcium channels (Calcium – dependent SNARE protein)

Source

- Clostridium botulinium
- Bacterial toxin
- Type A → H
- In humans Type A > type B is effective
- Type A- BTX-A is used as a drug

Preparations

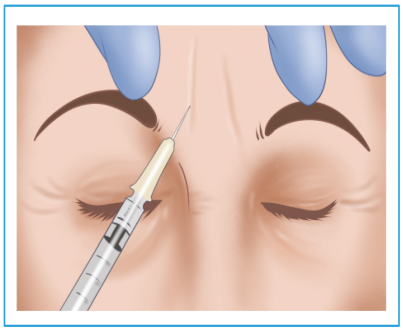
- Type A is made longer acting by adding certain lipid molecules or moiety
  - Onabotulinum Toxin A
  - Abobotilinum Toxin A
  - Incobotilinium Toxin A

Precautions

- Botulinum toxin is the most lethal toxin to mankind
  - 1 mg can kill 1 million people
- Inj. BTX-A must produce an effect at the local site only
- Prevent cause of death is respiratory paralysis

Uses

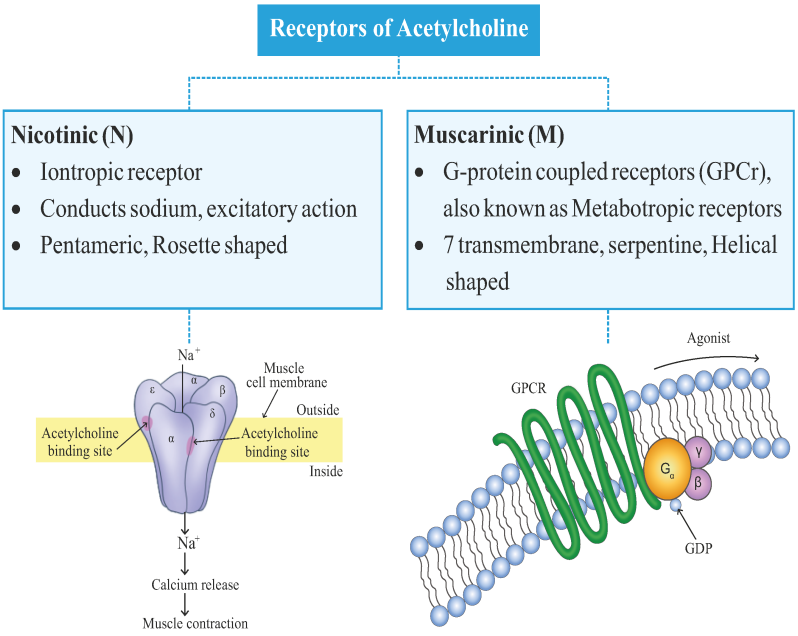
ACh actions	Botulinum toxin uses
Increase muscle contraction	**Relieve Muscle spasticity (rigidity)** • **Blepharospasm:** Eyelids not opening • **Achalasia:** Dysphagia due to LES spasm • **Torticollis / Wry neck:** Sternocleidomastoid muscle rigidity • **Squint:** Contraction of one eye, both eyes are not in coordination causing double vision
Increase pain sensation	Relieve migraine pain
Increases sweating	For the treatment of hyperhydrosis
	For cosmetic procedures - Reduces wrinkles



Botox injection given for glabellar lines or wrinkles

Receptors of Acetylcholine

00:37:52



Nicotinic receptors

00:40:00

Type	Nn	Nm
Location	Neurons (Ganglionic receptors) • SNS ○ Epinephrine ○ Norepinephrine • PSNS ○ Acetylcholine • **Adrenal medulla** ○ Epinephrine	Skeletal muscles • Muscle contraction occurs following sodium entry into the muscle and depolarization Part of the Somatic Nervous System • Voluntary actions
Subunits- 5	• All are α, β	• α, β, γ, δ, ε
Agonist	• Nicotine	• Nicotine
Antagonist	Ganglionic blockers • Hexamethonium • Mecamylamine • Trimethaphan	Non-depolarising muscle relaxants • Tubocurare • Atracurium • Vecuronium

Muscarinic receptors

00:46:25

- 5 types: M1→M5

	M1, M3, M5	M2, M4
Type	Gq type GPCR (Excitatory)	Gi type GPCR (Inhibitory)
Secondary messenger	Increase Calcium	Decreases Calcium

Location of muscarinic receptors

- **CNS**
  - M1 receptors are predominant

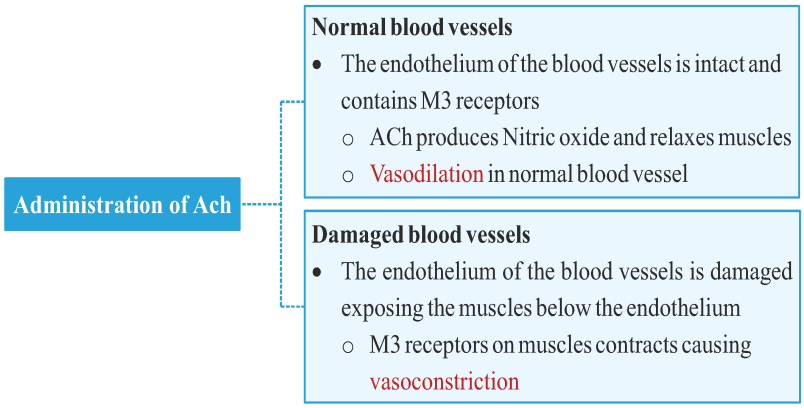
Hippocampus	Basal ganglia	Cerebral area
• ACh increase memory (cognition) • ACh used in treating Alzheimer's disease ○ Cholinergic drugs are given	• ACh decrease dopamine levels • In Parkinson's disease dopamine levels are to be increased ○ Anticholinergic drugs are given	• Ach induce seizures

- **Periphery**

Type	Periphery location	Effect	Agonist	Antagonist
M1	Stomach	Increase HCl production • Excitatory	Oxotremorine (Research purpose)	Treat peptic ulcers: Pirenzapine Telenzepine
M2	Heart	Reduce HR • Inhibit SA, AV node	Methacholine	-

M3	The rest of the body • Glands • Endothelium of blood vessels • Smooth muscles	Increase excitation • Increase sweating, lacrimation, and salivation (except bile) • Produce Nitric oxide (EDRF) → vasodilation Contraction • Blood vessels: Vasoconstriction • Bladder: Urination • Bronchus: Bronchospasm /asthma • Intestine: Diarrhea • Iris: Miosis (contraction of sphincter pupillae)	Bethanechol (Contracts bladder leading to Urinary retention)	Solifenacin Darifenacin (Relax bladder)

- Nitric oxide is also known as EDRF (Endothelium-derived factor)

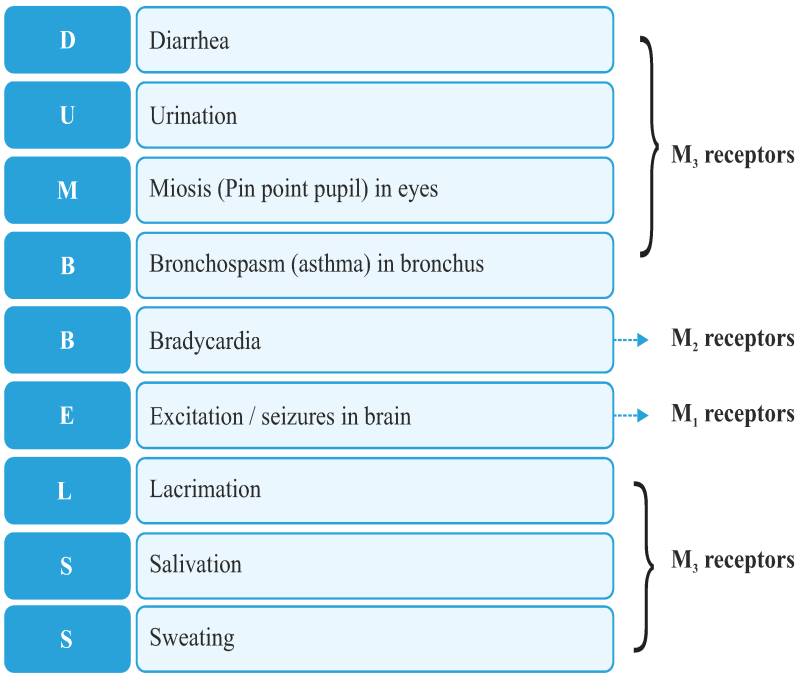


Summary

01:00:35

Effect of Acetylcholine in body

- Increase all secretions in the body



14 CHOLINERGIC DRUGS

- Cholinergic drugs are also known as Parasympathomimetics as these drugs increase the action of ACh and in turn, increase the activity of parasympathetic nervous system activity.
- Common Effect: DUMBBELSS
  - **D**iarrhea
  - **U**rination
  - **M**iosis
  - **B**ronchospasm
  - **B**radycardia
  - **E**xcitation/ seizures
  - **L**acrimation
  - **S**alivation
  - **S**weating

PYQ: FMGE 2020

PYQ: NEET PG 2023

00:01:55

Types of Cholinergic Drugs

Directly acting

- They are receptor agonist that stimulates nicotinic and muscarinic receptors
- **2 types**
  - Choline Esters
  - Alkaloids (natural)

Indirectly acting

- Inhibitors of anticholinesterase
  - Inhibits degradation of Ach
  - Increases the level of endogenous Ach
- **2 types**
  - Carbamates
  - Organophosphates

Directly Acting Cholinergics

00:04:50

Esters

- These are synthetic drugs
- These drugs contain- CHOL in them.

Acetylcholine	• Shortest acting drug
	• Rapidly degraded by Pseudocholinesterase
	• M_3 agonist
	• Given as topical eye drops
	  ○ Produces transient miosis
	  ○ Used to check the responsiveness of the iris during ocular surgery

Bethanechol	• Long-acting drugs PYQ: FMGE 2022
	• Resistant to degradation by Pseudocholinesterase
	• Given for urinary retention
	  ○ Postoperative bladder atony
	  ○ Postoperative paralytic ileus (constipation)

Carbachol	• Long-acting drugs • Resistant to degradation by Pseudocholinesterase • Used as eye drops to produce miosis in glaucoma patients

Methacholine	• M_2 agonist • Methacholine challenge test- Used as inhalation to provoke asthma

Normal Patient	In asthmatic patient
Bronchus is normal	Hypertrophy or hyperresponsive muscles (Contain all receptors)
Bronchus contains M_3 receptor	Methacholine provokes asthma
Inhalational methacholine acts on the M_2 receptor	Diagnoses asthmatic patient
No effect on M_3 receptors	Other tests: Histamine challenge test, Mannitol challenge test

Alkaloids

00:12:40

- Found in nature
- **Note: Mnemonic-** PAN Masala

Pilocarpine	• 2nd shortest acting drug obtained from the Pilocarpus plant
	• Used as topical eye drops(0.5-4%)
	• Available as Ocusert: Implant in the eye
	• DOC as a Miotic agent as it causes pupil constriction
	• Used in glaucoma to counteract the effect of mydriatics after fundoscopy
	• Break adhesions of iris: Synechiae
	• Diagnostic use: increased salivation, lacrimation
	• DOC for Xerostomia (dry mouth), Xerophthalmia (dry eyes)
	  ○ Sjogren syndrome
	  ○ Cystic fibrosis
	  ○ Radiotherapy
	• Cevimeline is a similar drug with similar uses
	• Pilocarpine is never given orally or IV as it can provoke seizures

Arecholine	• Present in Areca nuts/ betel nuts
Nicotine	• Present in the Tobacco plant PYQ: FMGE 2022 • Use: Smoking cessation
Muscarine	• Present in Poisonous Mushroom

Smoking De-addiction

00:19:40

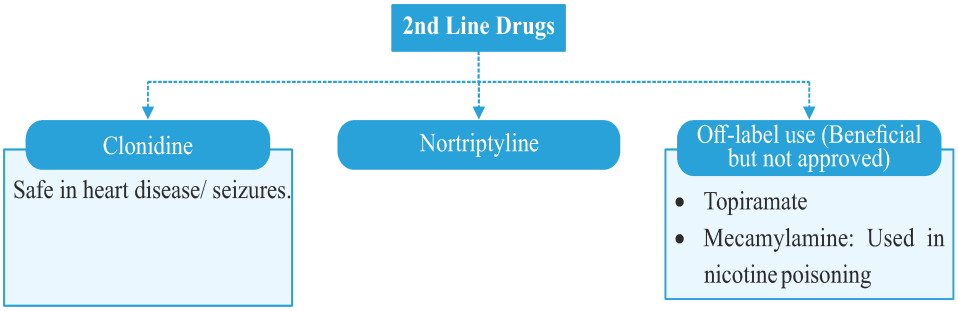
- **Note: Mnemonic-** Nicotine Very Bad

1st Line Drugs

Nicotine
- Transdermal patch
- Nasal spray
- Chewing gums
- Lozenges
- Never given orally, sublingual due to its fast absorption
- Contraindicated in heart diseases (HTN, MI, angina), seizures

Varenicline
- Partial agonist at nicotinic receptor
- Contraindicated in heart diseases (HTN, MI, angina), seizures
- Side effects: Depression (Suicides)
- Used in tobacco chewing

Bupropion
- Agonist at nicotinic receptor
- Antidepressant: NDRI (Norepinephrine dopamine reuptake inhibitor)
- Contraindicated in heart diseases (HTN, MI, angina), seizures



- Most effective treatment
  - Psychological makeup: Cold-Turkey technique
- Most effective drug: Varenicline

Mushroom Poisoning

00:27:18

	Early Mushroom Poisoning	Late Mushroom Poisoning (Phalloides type)	Hallucinogenic Type
Species	• Inocybe	• Amanita Phalloides	• Amanita Muscaria
Toxin	• Muscarine	• Amatoxin	• Muscimol
Symptoms	• DUMBBELSS	• Hepatotoxicity (most dangerous)	• Hallucinations, seizures

Antidote	• Atropine (blocks muscarinic receptor)	• Hepatoprotectives
		  ○ Thioctic acid
		  ○ Silibinin
			• Supportive treatment
			• Contraindication :Atropine

Indirectly Acting Cholinergic Drugs

00:31:45

- Also known as Anti-cholinesterase
- Inhibit acetylcholinesterase <<< Pseudocholinesterase
- Increase the level of endogenous Ach

Reversible Anti-cholinesterase
- Used clinically
- Carbamates
- Tacrine

+

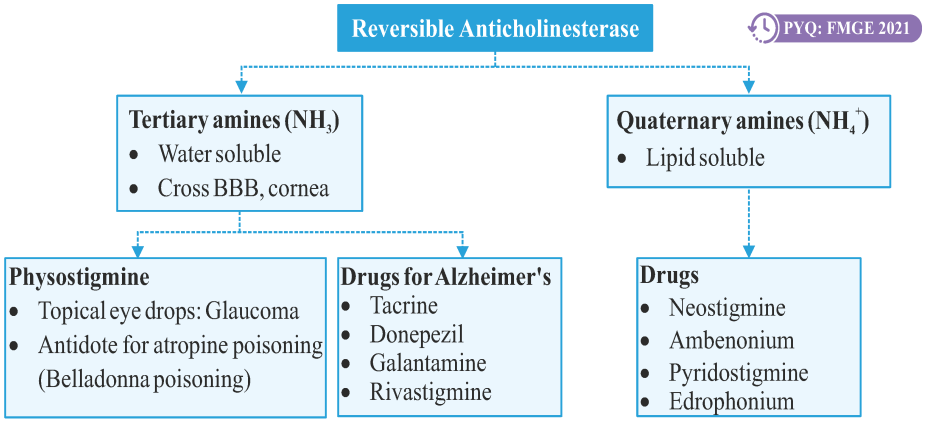
Irreversible Anti-cholinesterase
- Used in poisons
- Organophosphates
- Also known as Suicide inhibitors, Hit & Run drug

=

Anti-cholinesterase drugs

Reversible Anti-cholinesterase

00:34:50



Drugs for Alzheimer's Disease

00:39:30

- Patients with Alzheimer's disease suffer from dementia (Memory/ Cognitive loss). PYQ: INICET 2022

Anticholinesterases are the first-line drugs in the treatment of Alzheimer's disease

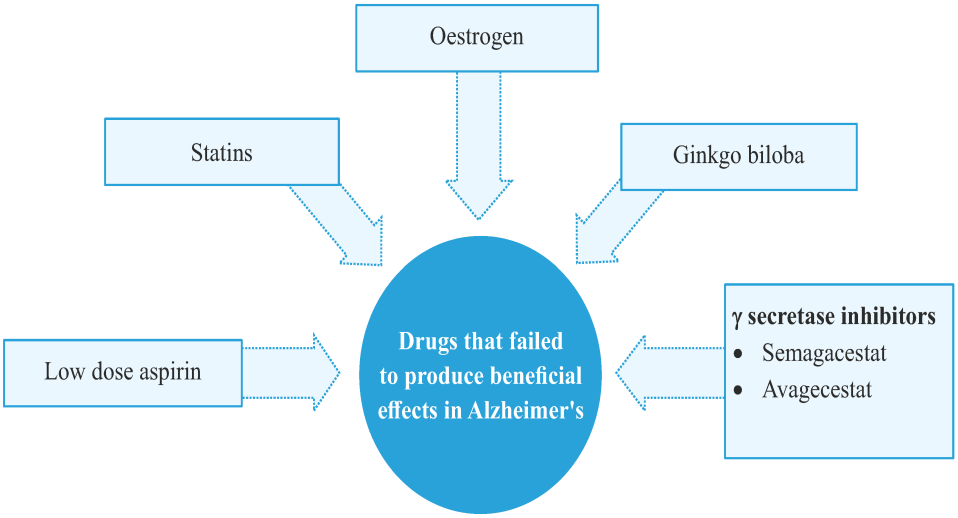
- Tertiary amines: Increase ACh in the brain improving the memory

→

- **Tacrine**: It is banned as it is Hepatotoxic
- **Donepezil**: DOC as it is the longest-acting and most effective
- **Galantamine**
- **Rivastigmine**: Available as transdermal patch

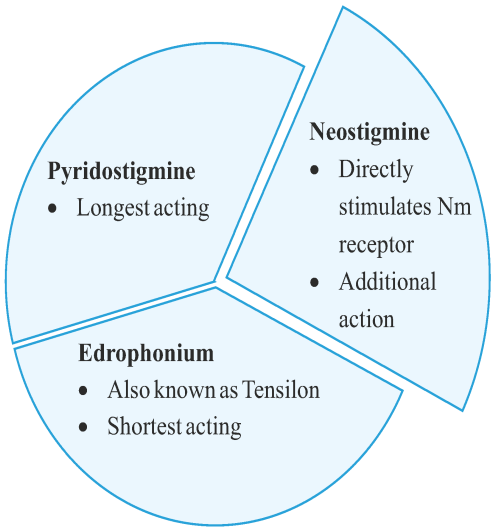
For Severe dementia (Uncontrolled by Anti-ACh)

- **Memantine** PYQ: FMGE 2023
  - NMDA antagonist
  - Increases memory in Alzheimer's
- **Aducanumab:** Monoclonal antibody against β_1 amyloid
- **Lecanemab:** Recently approved



Quaternary Amines

00:46:35



Uses

Cobra bite poisoning

- Venom blocks Nm receptor causing muscle paralysis and respiratory depression
- DOC: Antivenom
- Neostigmine is added if muscle paralysis sets in

Curare (muscle relaxants)

- Blocks Nm receptor
- Leads to postoperative muscle paralysis
- DOC: Neostigmine

Myasthenia gravis

PYQ: FMGE 2022, FMGE 2021

- Antibodies block Nm receptor
- Muscle paralysis
- DOC: Neostigmine

Side effects of Neostigmine

- Increase ACh levels by stimulating nicotinic and muscarinic receptors and produce DUMBBELSS side effects.
  - Bradycardia
- Neostigmine is given along with atropine as it blocks muscarinic receptor

Myasthenia Gravis 00:52:58

Pathophysiology

- Myas: muscle; asthenia: weakness
- An autoimmune disease in which antibodies block Nm receptor leading to muscle paralysis and weakness

Muscles involved

- Most common muscle involved: Ocular Muscles (Ocular myasthenia gravis) > Hands and feet
- Most Resistant muscle involved last is the Diaphragm

Symptomatic treatment

- Improve weakness
- Stimulate Nm receptor
- Overcome Nm blockage
- DOC: [Pyridostigmine (OD) > Neostigmine (QID)] + Atropine
- Edrophonium: Used in diagnosis of Myasthenia gravis PYQ: FMGE 2021
  - Tensilon test

Tensilon test

- In a patient with Ocular myasthenia gravis with ptosis, inj. Edrophonium administration improves ptosis by increasing ACh and reducing weakness.
- This is an ameliorative test for the diagnosis of Myasthenia gravis

Myasthenia gravis | After injection of 10mg edrophonium

- Provocative test with Tubocurare blocks Nm receptor and the symptoms worsen. It is a dangerous test that causes respiratory depression.

Definitive Treatment

- Ocular MG: Immunosuppressive drugs
- Generalized MG with associated Thymoma: Drugs + Thymectomy

Immunosuppressive drugs

As induction → Shift to Azathioprine → Azathioprine resistant cases

- Prednisolone
- Methylprednisolone

- As maintenance
- Steroid sparing effect

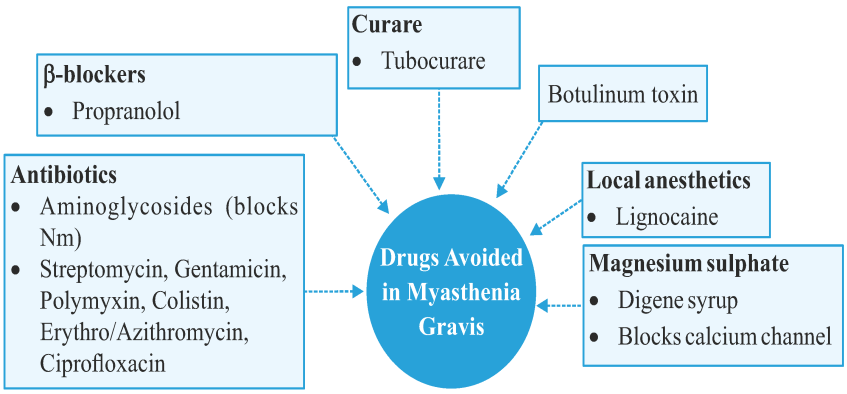
- Cyclosporine
- Tacrolimus
- Rituximab

PYQ: INICET 2021

Myasthenic Crisis

- Emergency
- Respiratory suppression
- Inj. Neostigmine + Atropine
- Remove antibodies by plasmapheresis
- IV-IG: Neutralise antibodies

- **Note: Mnemonic-** ABC BALMA



Snakebite Poisoning 01:08:14

- **Cobra and Krait**
  - Neurotoxic venom
  - Blocks Nm
  - Muscle paralysis
- **DOC:** IV polyvalent antivenom
  - Add neostigmine/edrophonium along with atropine

Irreversible Anti-cholinesterase 01:10:25

- Mainly used as poisons (insecticides)

Carbamates	Organophosphates (OP)
• Carbaryl • Aldicarb • Propoxur	• Malathion • Parathion • Sulthium • Diazinon (TIK-20) • Chlorpyrifos

- Propoxur + Chlorpyrifos
  - Baygon
- Nerve gas
  - Tabun
  - Sarin
  - Soman

Important Information
Endrin is an Organochlorine

Carbamates and Organophosphates Poisoning 01:13:50

Clinical features

- Increased Ach
  - DUBBELSS + Red tears
  - Pinpoint pupil
  - Damaged RBC esterase- Hemolysis

Mechanism of action

Inhibits Pseudocholinesterase > anticholinesterase

Diagnosis

- Clinical based
- Activity of Pseudocholinesterase and anticholinesterase- Reduced activity

Cholinesterase enzyme degrading Ach

- U-shaped CHE has
  - Anionic site(attachment)
    → ACh attaches
  - Esteratic site (hydrolyse)
    → Breaks and degrades ACh

- OP blocks the esteratic site
- Carbamates block both anionic and esteratic site
- Tacrine and Edrophonium
  - Blocks Anionic site only

Reason OP poisoning is more dangerous

- Out of 5 organic groups, 2 groups are attached to esteratic site.
- Prolonged duration leads to separation of organic groups and it is harder to remove only the phosphate and estertic bond.
- This permanent or irreversible attachment of phosphates to esteratic site is known as ageing of enzymes.
- Oximes cannot separate the phosphate and esteratic bonding if the enzyme has undergone aging.

Treatment

OP Poisoning	Carbamate Poisoning
• Block ACh receptor ○ DOC: Atropine	• DOC: Atropine
• Cholinesterase reactivator ○ Oximes	• Contraindication: Oximes

Atropine

- Overall DOC for Carbamate and OP poisoning
- Life-saving drug as it reverses the symptoms of DUMBBELSS
- Dose: 2 mg/kg/IV
  - Repetitive injection till Atropinization
- **Atropinization**
  - Mydriasis
  - Tachycardia
  - Constipation: Reduced bowel syndrome
  - Dryness of respiratory secretions- Definitive sign of atropinization

Oximes

- Cholinesterase enzyme reactivators
- Binds to anionic site and remove OP from esteratic site
- Given in early OP poisoning
- Ineffective in late OP poisoning- Aging of enzyme
- Contraindicated in Carbamate poisoning
  - As the anionic site is already blocked
- **Drugs**
  - Pralidoxime (PAM): Can't cross BBB
  - Obidoxime: Can't cross BBB
  - Diacyl monoxime (DAM): Can cross BBB and is most effective

Chronic OP Poisoning

- Occupational hazard
- Low-dose chronic exposure to OP leads to demyelination of neurons (Permanent damage)
- No treatment

15 ANTI-CHOLINERGIC DRUGS

- Anticholinergic drugs block acetylcholine receptors

Acetylcholine receptors

Muscarinic receptors
- Drugs that block muscarinic receptors – Antimuscarinic drug.
- Antimuscarinic drugs are known as anticholinergic drugs

Nicotinic receptors

N_N- Nicotinic neuronal
- N_N receptors are present on ganglia, both sympathetic and parasympathetic ganglia
- Drugs that block N_N receptor- Ganglionic blockers

N_M- Nicotinic muscular
- N_M present on skeletal muscle
- Drugs that block N_M receptor – Non-depolarising muscle relaxants
  - Drugs end with curare- Tubocurare
  - Ends with curium- Atracurium
  - End with curonium- Vecuronium

Antimuscarinic drugs

00:02:28

PYQ: FMGE 2021

Antimuscarinic drugs

Natural drugs
- **Atropine-** Obtained from Atropa belladonna or Datura plant
- **Hyoscine (scopolamine)-** Obtained from Hyoscyamus niger plant/Scopol plant

Synthetic drugs (rest all drugs are synthetic)

Other classes of drugs
- Drugs that also possess anticholinergic effect
- Blocks muscarinic receptors
- **Note:mnemonic- ATAQA**
  - A - Antihistaminic drugs
  - T - Tricyclic antidepressants (Imipramine)
  - A - Antipsychotic drugs (Chlorpromazine)
  - Q - Quinine
  - A - Amantadine

Important Information
- Belladonna means beautiful lady
- In the early days, women used to eat the Atropa belladonna plant to look beautiful as it produced mydriasis and reduced sweating.

Features of atropine poisoning

00:05:56

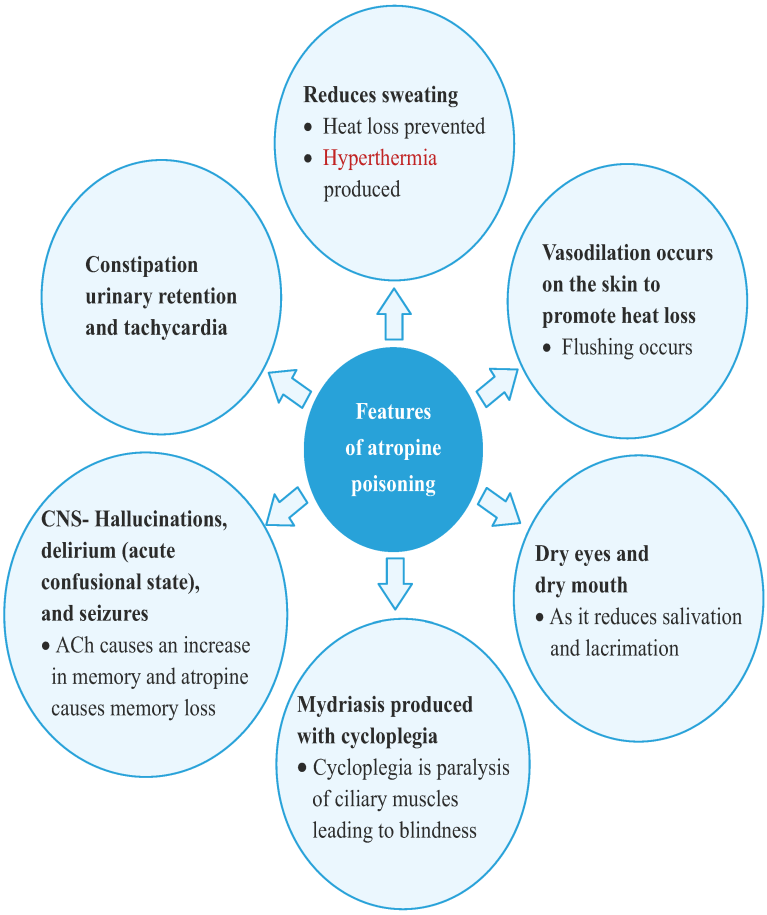
Datura flower shaped like a trumpet

- Acetylcholine muscarinic receptors produce symptoms of DUMBBELSS – all body secretions increase
  - **D** - Diarrhea
  - **U** - Urination
  - **M** - Miosis
  - **B** - Bradycardia
  - **L** - Lacrimation
  - **S** - Sweating
  - **S** - Salivation

PYQ: NEET PG 2023

PYQ: FMGE 2021

- Atropine blocks acetylcholine muscarinic receptors and produces features opposite of DUMBBELSS



Important Information

- Most common feature of atropine poisoning in children is hyperthermia
- Most common feature of atropine poisoning in adults is dry eyes and dry mouth

- **Famous poem about atropine –**
  - Hot as hare (hyperthermia)
  - Red as a beat (flushes)
  - Dry as bone
  - Blind as bat
  - Mad as hatter

Management of atropine poisoning

00:11:15

- Antidote - Physostigmine
  - Increase the acetylcholine level in the body
  - Physostigmine is a tertiary amine and crosses the blood-brain barrier reversing the atropine effect on CNS.
  - Whereas, Neostigmine cannot cross BBB so it is not used in atropine poisoning

Effect of anticholinergic drugs body

00:13:00

Central nervous system

Cortex	• When released, acetylcholine increases memory in the cortex
	• Among atropine and hyoscine, hyoscine has better Blood Brain BArrier entry
	• Atropine decreases memory/cognition
	  ○ Decreases cognition
	  ○ Cause excitation – seizures
	• Hyoscine decreases memory/cognition
	  ○ Cause sedation (calm and sleepy)
	• Hyoscine is used in the interrogation of criminals: Narcoanalysis
	  ○ Hence known as truth serum
	• DOC for narcoanalysis is thiopentone (barbiturates)
	• Anticholinergic drugs are contraindicated in Alzheimer's disease

Basal ganglia	• Increased acetylcholine leads to a fall in dopamine levels PYQ: FMGE 2019
	• Reduction in dopamine leads to Parkinson's disease
	• Drug-induced parkinsonism is caused by drugs blocking D_2 receptors in basal ganglia
	• In the treatment of drug-induced Parkinsonism
	  ○ Levodopa can not be used
	  ○ Reduce the action of acetylcholine choline using anticholinergic drugs and antihistaminic drugs
	• Anticholinergics
	  ○ Benzhexol (trihexyphenidyl)
	  ○ Benztropine
	  ○ Biperiden
	• Antihistaminic drugs
	  ○ Promethazine
	  ○ Diphenhydramine

Vestibule (inner ear) 00:21:05

Vestibule is connected to 3 semicircular canals

↓

Inside semicircular canals, endolymph is present

↓

When head rotates endolymph in the ear rotates

↓

Vestibular nerve is stimulated by the movement of endolymph

↓

On vestibular nerve M_1 and H_1 receptors are present

↓

Nerve goes to cerebellum from there to vomiting center – CTZ area

↓

Stimulation of CTZ causes nausea and vomiting

↓

Motion sickness

Drugs

- Antimuscarinic and antihistaminic drugs are used in the treatment of motion sickness
- **Antimuscarinic drug** – Hyoscine
- **Antihistaminic drug** – 1st generation antihistamine (can cross BBB)
  - Diphenhydramine
  - Promethazine
  - Cyclizine
  - Meclizine
  - Cinnarizine

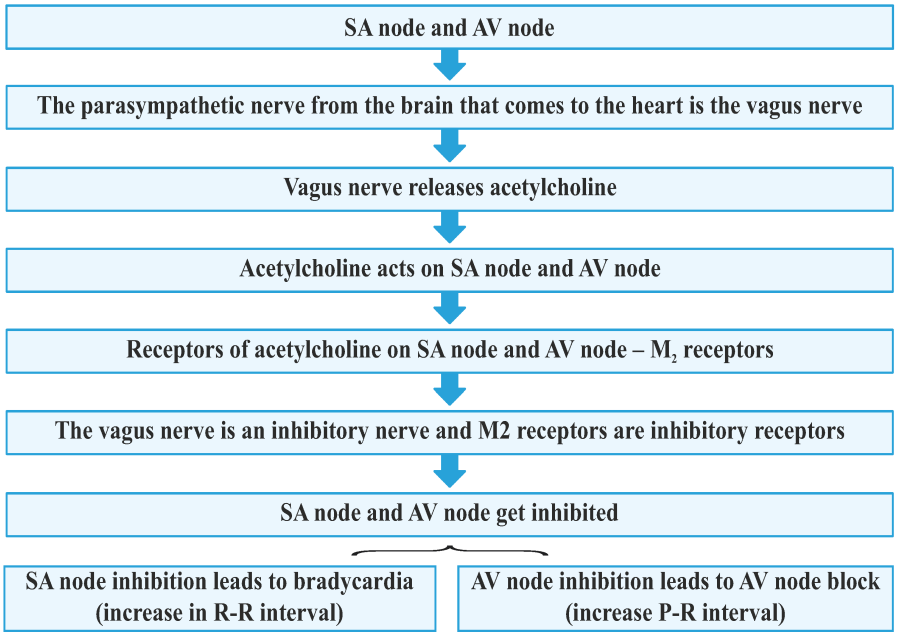
ROA

- All given as oral form
- Hyoscine and diphenhydramine can also be given as transdermal patch
- Transdermal patch attached behind pinna (posterior auricular area)
  - Drugs must be taken at least 30 minutes before journey
    - → Only for prevention of motion sickness
    - → Not effective if vomiting has started
    - → Block vestibular nerve before it trigger CTZ
    - → If vomiting already started, let the patient vomit and then give drugs that can prevent another episode

Side effects

- Sedation
- Ephedrine is added to prevent sedation – But ephedrine do not prevent nausea and vomiting in motion sickness

Heart 00:27:50



- DOC: Treatment of any node block is atropine
  - Atropine is used for the treatment of bradycardia and AV node block
  - Because atropine blocks M_2 receptors of the SA node and AV node and prevents the SA and AV node block
  - Atropine for bradycardia is not effective in a transplanted heart as it is a denervated heart (no vagus nerve)

Q. What is the effect of Atropine on heart rate

Ans.

- Atropine on IV produces short-lasting Bradycardia (Transient)
- Later on, produces long-lasting Tachycardia (main effect)

Explanation

- The heart receives the vagus nerve and stimulation of M_2 receptors reduces the heart rate.
- Atropine blocks postsynaptic M_2 receptors in the heart, preventing Bradycardia.
- In the vagus nerve, M_1 receptors are present that are presynaptic and inhibit the release of Ach.
- Atropine first blocks M_1 receptors on the vagus nerve, increases ACh release and decreases heart rate.

Respiratory tract 00:34:00

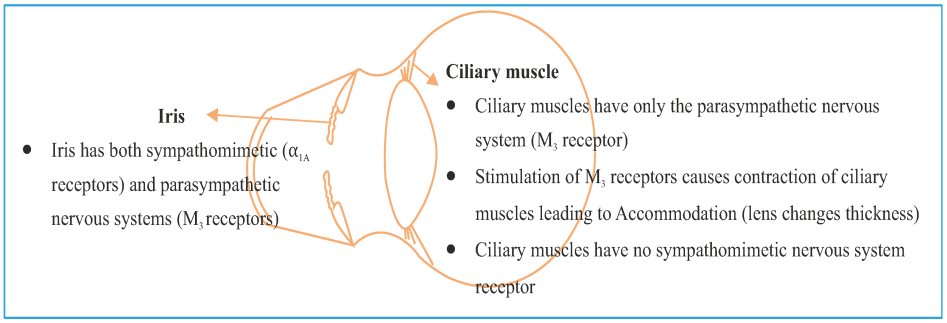
- On the large bronchus, M_3 receptors through the vagus release ACh leading to mucus secretion and bronchoconstriction
- Anticholinergics block M_3 receptors causing dry bronchus and dilated bronchus
- Drugs

Oral and IV	Inhalational

• Atropine, Hyoscine: Tertiary amines (NH_3)
• Glycopyrrolate: Quaternary amines (NH_4^+)
• Given before intubation, insertion of Endotracheal tube
• During surgeries to reduce bronchial secretions to reduce the risk of aspiration
• Glycopyrrolate does not cross BBB- The most preferred drug during surgery
	• Given in COPD and asthma as they are bronchodilators
	• Ipratropium, Tiotropium, Oxytropium
	• Newly approved drugs
	  ○ Umeclidinium
	  ○ Aclidinium
	  ○ Glycopyrrolate
	  ○ Revefenacin

Eyes

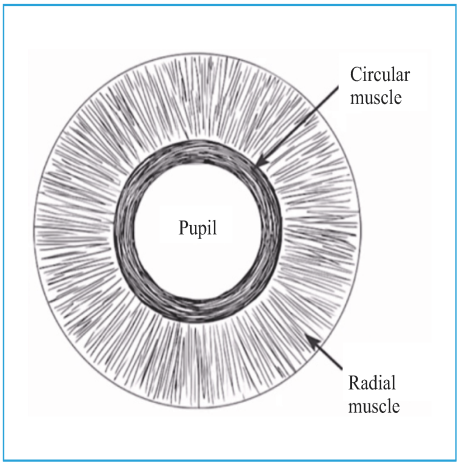
00:39:30



Iris has two muscles

Circular muscles
- Also known as Sphincter pupillae, Parasympathetic Nervous systems (M_3 receptors)
- Stimulation contracts muscles
- Active miosis

Radial muscles
- Also known as Dilator pupillae
- Sympathomimetic (α_{1A} receptors)
- Stimulation contract muscles
- Active mydriasis



- Anticholinergic action: Block M_3 receptors in the eye

Paralysis of ciliary muscles	Paralysis of sphincter pupillae
Also known as Cycloplegia: Loss of accommodation	Relaxed: Passive mydriasis

Uses:
• Refractive error testing
  ○ The lens behind the cornea reduces in thickness
• Ciliary spasm
  ○ Painful eye, inflammation
  ○ Anterior uveitis
	Uses:
	• Fundoscopy (to see retina)

Uses of anticholinergic drugs

Atropine
- Longest / most effective drug
- Duration: 14 days
- DOC in Anterior uveitis: To reduce ciliary muscle spasms and pain in the eye
- DOC in fundoscopy in children
  - 1% ointment is applied to produce mydriasis in children (More parasympathetic activity in children)
- Atropine is not used in refractive error testing as there is a loss of accommodation for 14 days

Homatropine
- Used in the treatment of uveitis

Topical eye drops

Cyclopentolate
- Used in refractive error testing due to short duration of action and also in the treatment of uveitits

Tropicamide
- Shortest acting
- Onset : 15 mins
- Duration: 3-6 hours
- Used in refractive error testing due to short duration of action and also in the treatment of uveitits

Phenylephrine
- Sympathetic drug (α_1 agonist) that contracts radial muscles
- Used in fundoscopy in adults to produce active
- Phenylephrine doesn't have Cycloplegic action
  - Ciliary muscles do not have α receptors, only muscarinic receptors are present
  - Not used in anterior uveitis and refractive error testing

Pilocarpine
- A cholinergic drug that stimulates M_3 receptors
- Used in the treatment of Glaucoma to produce active miosis
- Treatment of Glaucoma
- Side effects: Ciliary muscle spasms and painful eyes
- To relieve pain in anterior uveitis, cholinergic drugs are used

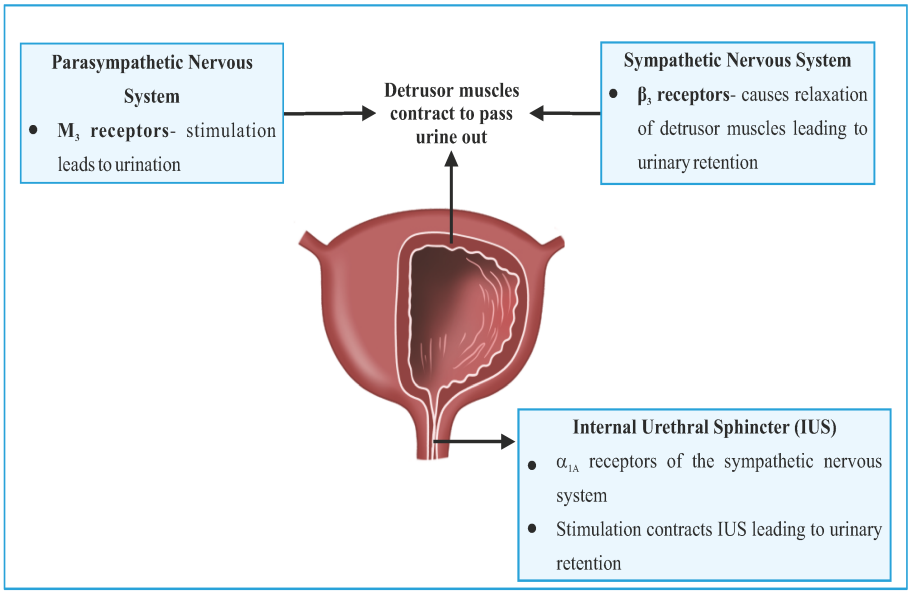
Important Information
- Atropine-like drugs are contraindicated in Glaucoma

Q. Shortest acting mydriatic
Ans. Phenylephrine
- Pure mydriatic
- No action on ciliary muscles

Q. Shortest-acting cycloplegic mydriatic
Ans. Tropicamide

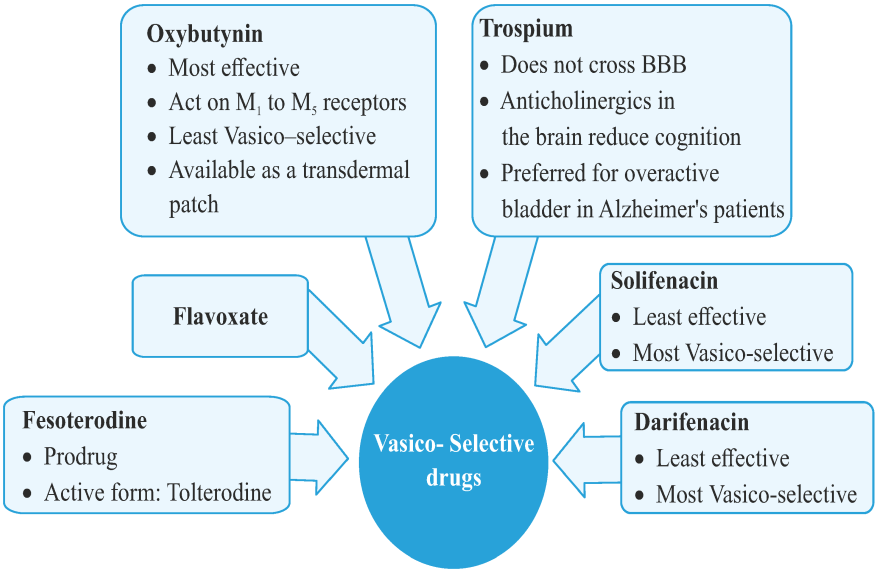
Urinary bladder

00:57:20

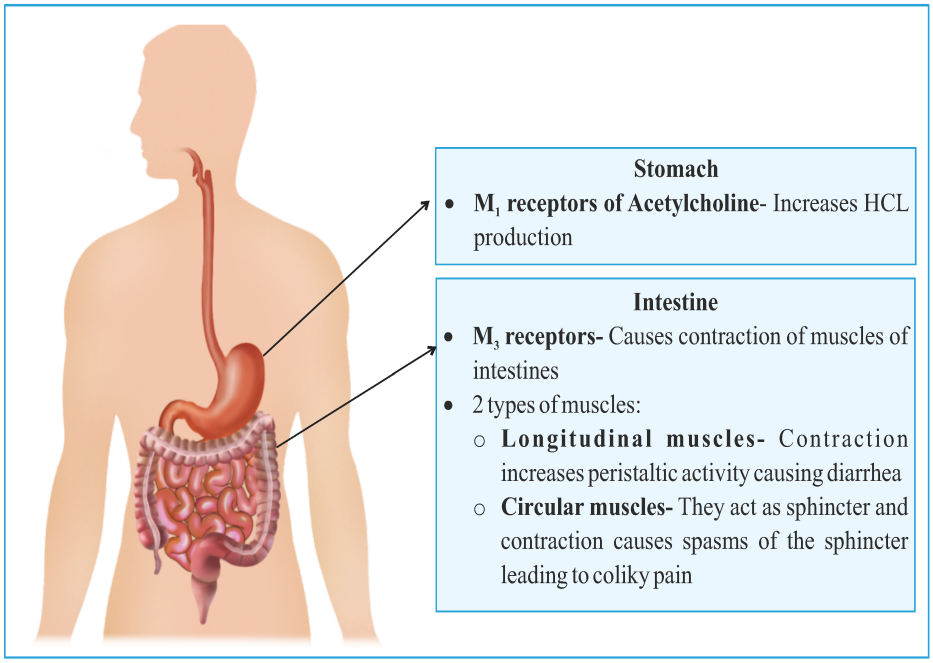


- Anticholinergic drugs block M_3 receptors and reduce detrusor contraction and are used in the treatment of overactive bladder
  - In an overactive bladder detrusor muscles become unstable, contract unnecessarily, and there is sudden passage of urine
  - Anticholinergic drugs that block M_3 receptors of bladder - Vasico- Selective drugs

- Note: Mnemonic - OFF To School Days



- Contraindications- Benign Prostate Hypertrophy
  - IUS is adjacent to the prostate gland
  - The patient already has urinary retention due to contraction of the Detrusor muscles
- New drug for overactive bladder:
  - β_3 agonist- Causes relaxation of detrusor muscles
    - → Merabegron
    - → Vebegron



Treatment of Gastric/Peptic ulcers

- M_1 blockers are used to decrease HCl production
  - Pirenzepine
  - Telenzepine

Anticholinergic drugs in the intestine, also known as Antimotility-Antispasmodic drugs

Tertiary amines (Lipid soluble)
- Dicyclomine (Dicycloverine)
- Valethamate
- Hyoscine

Quaternary amines (Water soluble)
- Propantheline
- Isopropamide
- Glycopyrrolate
- Hyoscine Butyl Bromide (Buscopan)

- Dicyclomine, Hyoscine butyl bromide, and Glycopyrrolate are given in the treatment of abdominal colicky pain
- Other antispasmodic drugs: Drotaverine (Drotin injection)
  - Phosphodiesterase 4 inhibitors
  - Increase cAMP and relax the sphincter

Q. Which painkiller is not given in Colicky pain?

Ans. Opioids

- Best pain killers but produce spasms of sphincters in GIT

Atropine summary 01:15:35

Uses	Avoid
DOC: • Carbamate/Organophosphate poisoning • Early mushroom poisoning • Bradycardia/AV node block **Add on drug to** • Neostigmine to prevent muscarinic effect in myasthenia gravis • Diphenoxylate (Opioids)- reduces addiction	**Geriatric patients** • Glaucoma: Produce mydriasis • Alzheimer's patients: Memory loss • BPH: Urinary retention • Constipation

Ganglionic blockers 01:18:10

- Block N_N receptors of Acetylcholine
- NN receptors are present in both pre and postganglionic nerves of SNS and PNS
- Ganglionic blockers reduce both Sympathetic and Parasympathetic activity
  - Hexamethonium
  - Mecamylamine
  - Trimethaphan
- Every organ receives both SNS and PNS, but one nerve supply is predominant for each organ.

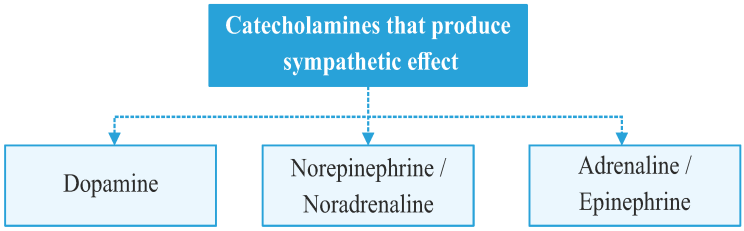
Organ system	Predominant nerves	Action of Ganglionic blockers
Heart	• PSNS (Vagus nerve)- Reduces heart rate	• Increase heart rate (Tachycardia)
GIT	• PSNS: Increases all secretions like diarrhea	• Constipation
Glands	• PSNS: Increases sweating, salivation, lacrimation	• Dry eye/ mouth
Bladder	• PSNS: Increased urination	• Urinary retention
Intestine	• PSNS: Diarrhea	–
Blood pressure	• SNS: Increase blood pressure	• Postural hypertension • Not atropine-like action
Penile erection	• PSNS: increase	• Block erection (impotence)
Penile ejaculation	• SNS: increase	• Block ejaculation (impotence)

Trimethaphan	Mecamylamine

• Used during arterial surgeries
• Aortic dissection
  ○ Block both SNS and PSNS supply
  ○ Aorta becomes non-responsive
	• Nicotinic receptors
	• Treatment of Nicotinic poisoning
	• Off label use – Smoking cessation

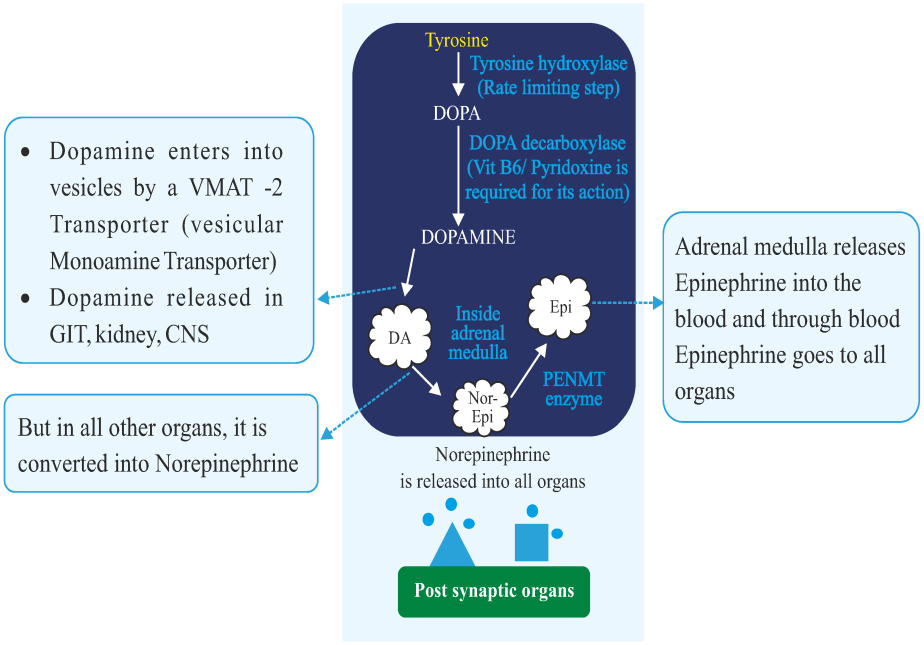
16 ADRENERGIC DRUGS PART-1

- Adrenergic drugs increase sympathetic activity in the body, hence they are also called sympathomimetic drugs



Synthesis of catecholamines 00:01:30

- Synthesized from an amino acid called Tyrosine



- Norepinephrine does not contain methyl group but Epinephrine contains methyl group
- PENMT enzyme- Phenylethanolamine N methyltransferase
- Released epinephrine and norepinephrine act on postsynaptic receptors
- Receptors of Epinephrine, Norepinephrine, and dopamine are α and β receptors (Sympathetic receptors)

Drugs acting on the pathway of synthesis of catecholamines 00:06:30

Metyrosine

- Inhibits rate limiting enzyme
- All catecholamine synthesis is inhibited
- Used to treat Pheochromocytoma (Inoperable)

Carbidopa and Benserazide

- Inhibits DOPA decarboxylase enzyme in peripheral neurons
- They are given along with Levodopa in Parkinson disease

VMAT inhibitors

- Inhibit entry of dopamine into vesicle leading to degradation of dopamine in cytoplasm
- Also known as Dopamine depletors

Irreversible VMAT inhibitors

- Reserpine
  - Causes depression leading to suicide
  - Hence, got banned

Reversible inhibitors

- Tetrabenazine
- Valbenazine
- They are used to treat Huntington disease
- DOC: Tardive dyskinesias (side effect of antipsychotic drugs)

Adrenergic neuron blockers

- Inhibits the release of catecholamines
- Guanethidine
  - Used to treat Hypertension
    → As catecholamines are sympathetic molecules – increases blood pressure
  - Rarely used nowadays because it causes severe postural hypotension

Reuptake and degradation

00:12:45

Reuptake	Degradation
• The action of Dopamine and norepinephrine is terminated by reuptake into the neurons • Dopamine is reuptaken by a transporter called DAT (Dopamine transporter) • Norepinephrine is removed by a transporter called NET (norepinephrine transporter) • Epinephrine is removed by the Liver with the help of ENT (extra neuronal transporter)	• Once the cathecolamines are reuptaken in to the neurons • MAO enzyme and COMT enzyme present in the neurons and liver degrade these catecholamines

- MAO (monoamine oxidase) and COMT (catechol O methyltransferase) enzymes by acting together degraded the catecholamines into Homovanillic acid and vanillylmandelic acid
- If they act
  - COMT acts on Epinephrine to convert it into metanephrine
  - COMT acts on norepinephrine to convert it into normetanephrine
- Diagnostic test for Pheochromocytoma
  - Pheochromocytoma is a tumor of sympathetic neurons producing excessive catecholamines that are degraded excessively.
  - Excessive levels of Homovanillic acid, vanillylmandelic acid, metanephrine, and normetanephrine in the urine is a diagnostic test for Pheochromocytoma

Reuptake inhibitors

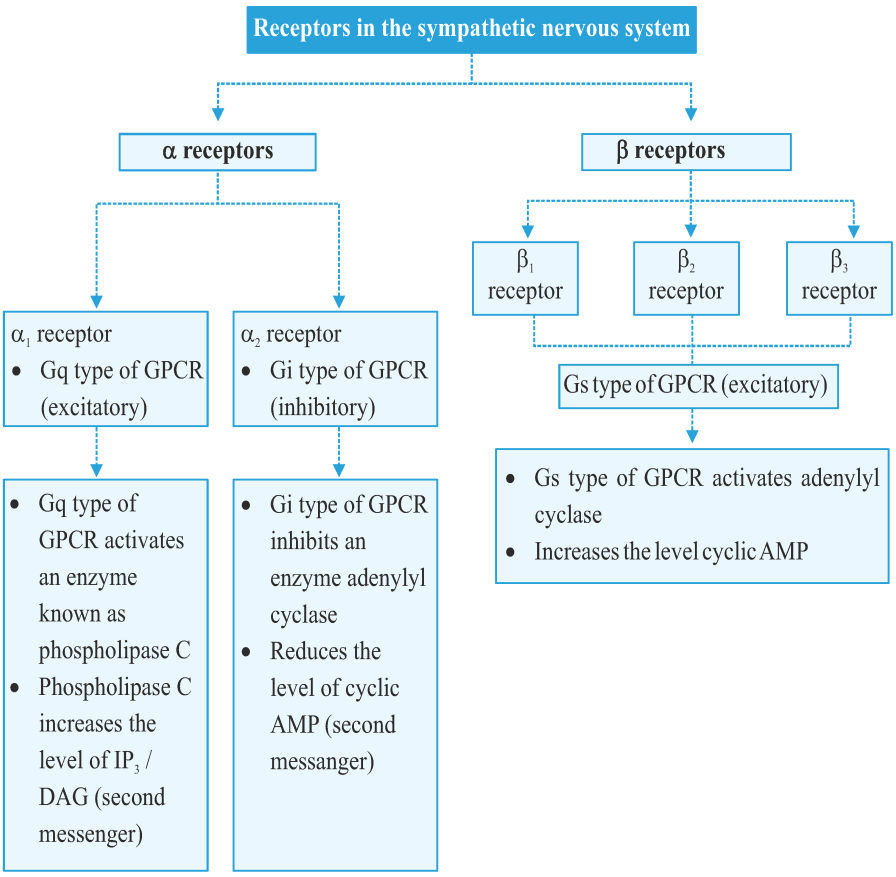
00:18:00

- The level of catecholamines remains high in the synapse area on inhibition of the reuptake of catecholamines producing long-term effects and increasing sympathetic activity

1. **Cocaine**
   - First local anesthetic
   - Increases sympathomimetic activity- Produces vasoconstriction (only local anesthetic to produce vasoconstriction)
   - Increases dopamine (Pleasure neurotransmitter)- Leads to addiction
2. **Antidepressants**

Sympathetic receptors

00:20:30

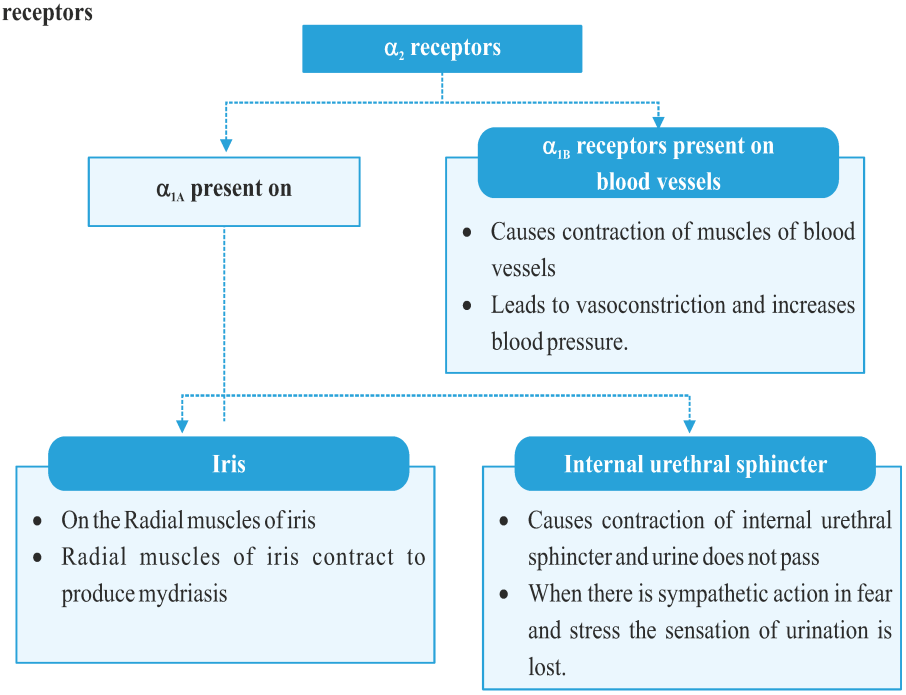


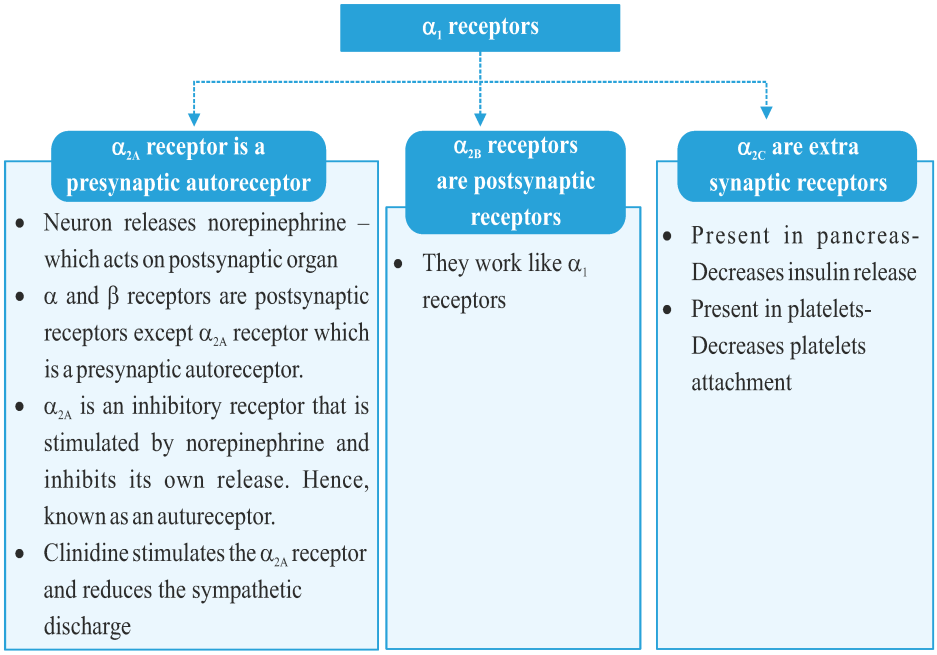
- α and β receptors both are G protein-coupled receptors
- A Scientist by the name of Ahlquist divided α and β receptors

Locations of receptors

00:23:50

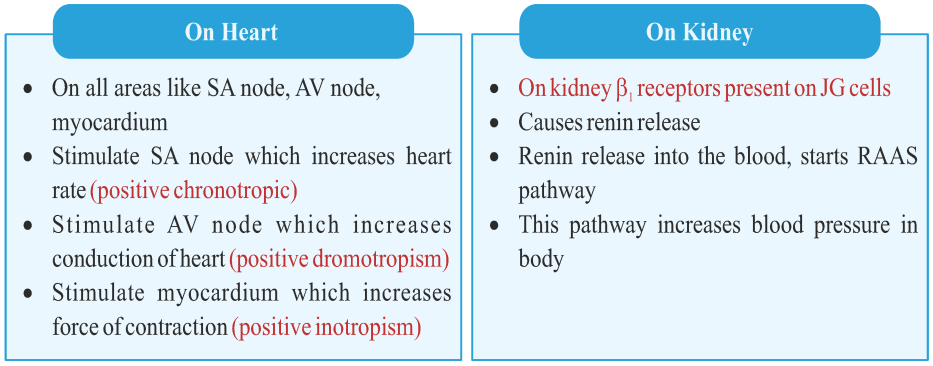
α receptors



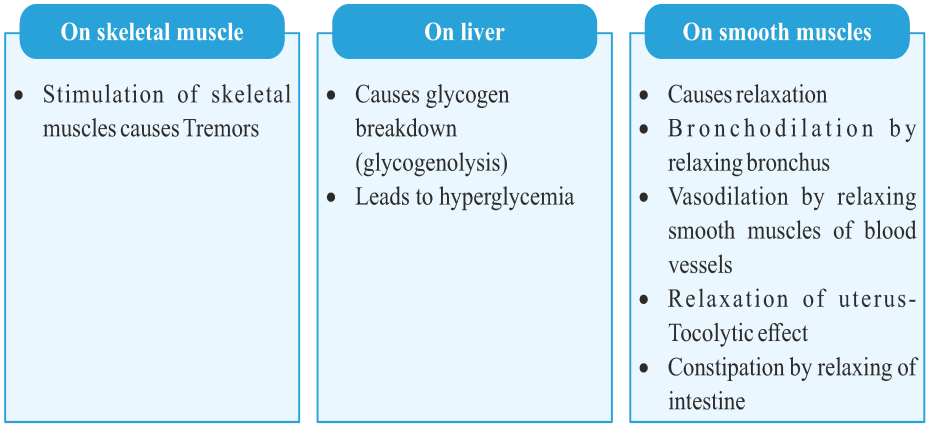


β receptors 00:31:10

- **β_1 receptors**



- **β_2 receptors**



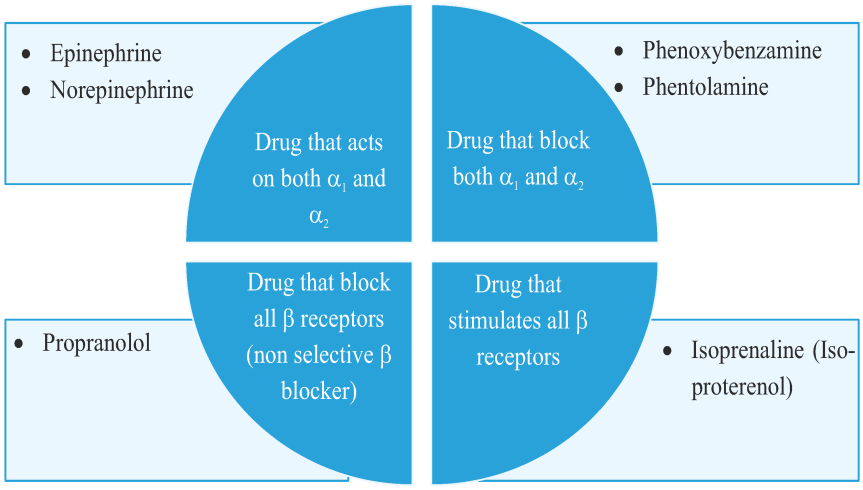
- **Salbutamol is β_2 agonist**
  → Bronchodilators used in asthma
  → Side effects – hyperglycemia, constipation, tocolytic action and vasodilation

- **β_3 receptors**
  - Present in adipose tissue and bladder
  - On bladder detrusor muscle
  - In adipose tissue lead to lipolysis
  - Bladder has both β_2 and β_3 receptors
    → Causes relaxation of the detrusor muscle decreasing the sensation of urination

Drugs Acting on Sympathetic Receptors

00:39:25

Agonist (stimulates receptor)	Receptors	Antagonist (blocks receptor)
Phenylephrine	α_1	Prazosin
Clonidine	α_2	Yohimbine
Dobutamine	β_1	Atenolol, metoprolol (cardioselective β blockers)
Salbutamol	β_2	Butaxamine
Merabegron	β_3	–



Adrenergic drugs

00:43:25

Classification

Directly acting	Indirectly acting	Mixed acting
• Directly go to receptors α and β • Stimulate the receptors as an agonist	• Increase the release of catecholamines like norepinephrine, epinephrine, etc.,	• Have both effects • They stimulate the receptors and also increase levels of Catecholamines
Two types of drugs • Catecholamines • Non-catecholamines	**Three types of drugs** • M - Modafinil • A – Amphetamine • T - Tyramine	**Two types of drugs** • M - Mephentermine • E - Ephedrine

Directly acting adrenergic drugs

Directly acting adrenergic drugs

Catecholamines

- Cannot be given orally
  - Because, in GIT, MAO enzyme degrades catecholamines
- Only by injections
- Used as an emergency medicine in the treatment of shock

Non catecholamines

- Can be given orally

Natural catecholamines

- Norepinephrine
- Epinephrine
- Dopamine

Synthetic catecholamines

- Dobutamine
- Isoprenaline
- Dopexamine
- Ibopamine
- Fenoldopam

Natural catecholamines

Norepinephrine 00:49:35

- Concentration of norepinephrine in the vial is 4 mg/4 ml equivalent to 1 mg/1 ml (Known as 1:1000)
- Stimulates α_1 and α_2 receptors
- Acts on β_1 and β_3 receptor
- Norepinephrine does not act on β_2 and hence does not produce bronchodilation and vasodilation

- **Uses of norepinephrine**

DOC: Cardiogenic shock

- Acute heart failure with hypotension (systolic BP < 85 mmHg)
- Norepinephrine stimulates
  - β_1 receptors – Increases the force of contraction on the heart
  - α_1 receptors – Increases blood pressure by vasoconstriction
- If it is cardiogenic shock without hypotension – Dobutamine is used
  - Acts only on β_1 receptors

DOC: Neurogenic shock/septic shock

- Neurogenic shock occurs because of trauma or some injury
  - Spinal cord and sympathetic nerves get damaged
- If patient have both bradycardia and hypotension –norepinephrine is used

Important Information

Norepinephrine is not used in anaphylactic shock

- The patient suffers from asthma in anaphylactic shock due to bronchoconstriction.
- To relieve this β_2 action is required but norepinephrine has no β_2 action

Epinephrine (adrenaline)

Surgery

00:55:10

- Acts on all receptors
- Has a weak action on β_3 receptors
- Concentration of vial of epinephrine – 1 mg/1 ml (1:1000)
  - Given as IM, Subcutaneous injection, ET – endotracheal
- If diluted, it becomes 0.1 mg/ml (1:10000)
  - Given as IV, IO (intraosseously) – tibia
- Epinephrine is never given intracardiac route as it damages muscles of the heart and causes myocardial necrosis

Surgery, Medicine

PYQ: INICET 2021

Epinephrine use	Dose and route	Rationale
Anaphylaxis (DOC)	0.5 ml of 1:1000 – IM route (Vastus lateralis)	• Epinephrine stimulates β_2 receptors – causing bronchodilation • Inhibits histamine release from muscles
Brittle asthma (sudden emergency in asthma)	0.5 ml of 1:1000 – IM or SC	• Epinephrine stimulates β_2 receptors – causing bronchodilation • Inhibits histamine release from muscles
Cardiac arrest (CPR)	1 ml of 1:10000 – IV or IO or 1 ml of 1:1000 – ET	• Epinephrine stimulates α_1 receptor– produces vasoconstriction and increases venous return to the heart • Norepinephrine, dopamine, and vasopressin – also are given in cardiac arrest
During or along with local anesthetics	1:50000 to 1:200000	• Epinephrine when given locally stimulates α_1 receptor– produces vasoconstriction and reduces the absorption of the local anesthetic into blood Note: Felypressin is an alternative drug used in local anesthesia.

- **Contraindication of epinephrine with local anesthetic**
  - In case of surgery on tip of an organ
    - → Avoid using epinephrine along with local anesthetic
    - → Because the tip of any organ contains end arteries
    - → If end arteries undergo vasoconstriction – it leads to ischemic necrosis
  - Examples
    - → Finger surgery (nail removal)
    - → Penile surgery
    - → Pinna surgery
    - → Nose tip surgery

Dopamine

01:07:10

- Concentration of dopamine in vial: 40 mg/ml
- Receptors
  - D_1 and D_2 receptors
  - Have norepinephrine-like effect (α_1, α_2, β_1 and β_3)
  - Does not act on β_2 receptors- Not used in anaphylactic shock
- Dopamine also increases the release of norepinephrine from the nerves
- Given only through IV – as a continuous IV infusion

PYQ: FMGE 2021

Dose of dopamine	Receptor action	Effect	Use	Side effect
Low dose 1-2 µg/kg/min	Stimulates D_1 and D_2 receptors Receptors -Present in blood vessels of the kidney	Vasodilation in the kidney- increases GFR	DOC - Acute renal failure or oliguria	Hypotension
Medium dose 2-10 µg/kg/min	β_1 receptors – present on the heart	Inotropic effect on heart – increase force of contraction	Acute heart failure	Arrhythmias (maximum arrhythmias)
High dose >10 µg/kg/min	α_1 receptor	Vasoconstrictio n -increase blood pressure	Shock (cardiogenic shock, septic shock, and neurogenic shock)	Hypertension

Q. Which dose of dopamine is not used in treating shock to increase blood pressure?

Ans. Low-dose dopamine

- Dopamine acts on D_1 and D_2 receptors causing vasodilation, hypotension, and worsening shock.

Q. Which receptors of dopamine are the most sensitive and least sensitive?

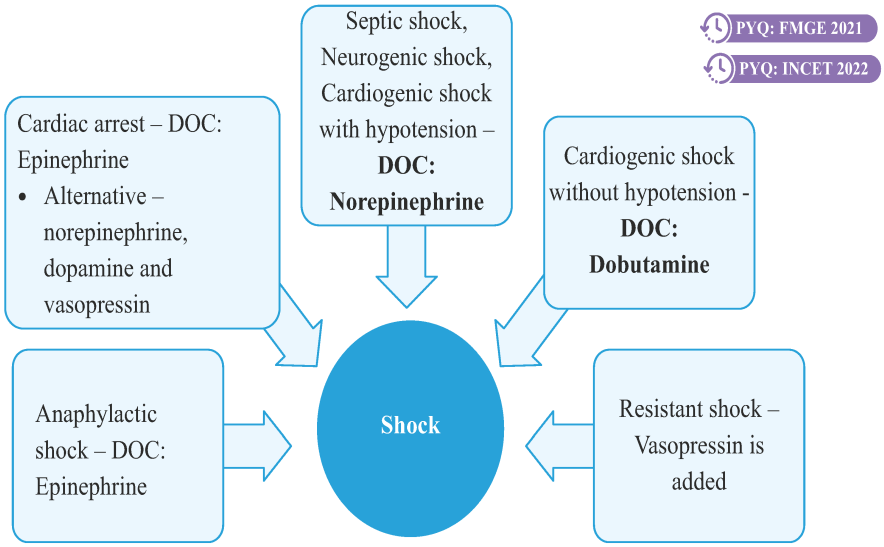
Ans.

- D1 and D_2 are the most sensitive receptors as they are stimulated at a low dose
- α_1 receptor is the least sensitive as they are stimulated at a high dose.
- Sensitivity: D1 and $D_2 > \beta_1 > \alpha_1$

Important Information

- When any catecholamine is used in the treatment of shock, clinical trials revealed that they do not reduce the mortality of patients.
- Catecholamines have no mortality benefits
- In turn, this increases the risk of intracranial hemorrhage/cerebral hemorrhage and sudden death

PYQ: FMGE 2021
PYQ: INCET 2022



Synthetic catecholamines

01:18:55

Drug	Receptor	Use
Dobutamine • Given IV • 2-8 µg/kg/min • $t_{½}$ is 2 mins	• Specific β_1 agonist • Negligible effect on blood vessels • Acts on both α_1 and β_2 – cancels the effect on blood vessels	• DOC: acute heart failure or cardiogenic shock without hypotension • DOC: stress echocardiography – to stimulate the heart and its contraction
Isoprenaline (Isoproterenol)	• Acts on β_1, β_2, and β_3 agonist	• Bradycardia • Asthma
Fenoldopam	• Partial D_1 agonist	• Oliguria with hypertensive emergency • Acute renal failure (ARF)
Ibopamine	• D_1 receptor and α_1 receptor agonist	• Oliguria/ARF • Mydriatic (eye drops)

Stress ECHO

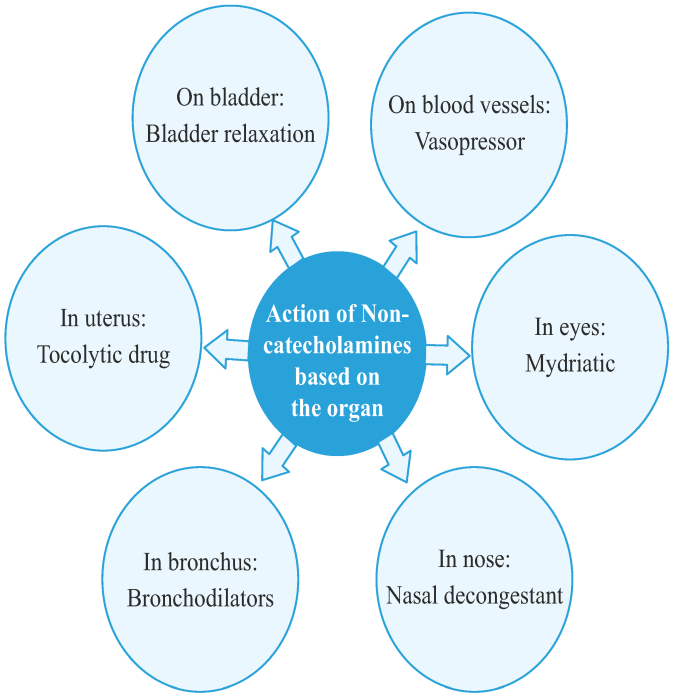
01:24:36

- In stress echocardiography, stress is put on the heart by administering various drugs to check the function of the heart
- Those functions include
  - Myocardial contractility
    → Dobutamine is given
  - Coronary blood flow
    → Adenosine – coronary dilator
    → Regadenoson – adenosine A_2 receptor
    → Dipyridamole – increase adenosine level

17 ADRENERGIC DRUGS PART-2

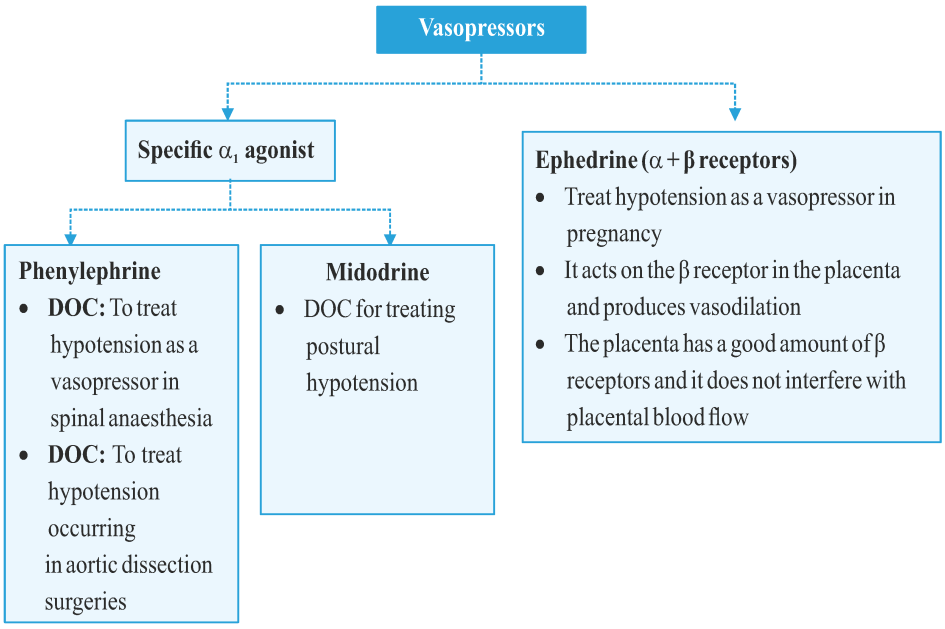
Directly acting adrenergic drugs- Non-catecholamines

- Given orally, IV, and topical



Vasopressors

- Blood vessels have α_1 receptor- Increases blood pressure by vasoconstriction
- Vasopressors are given in the treatment of hypotension



Mydriatic

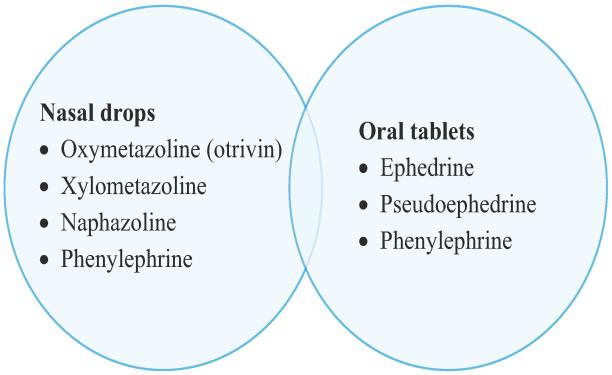
00:03:45

Phenylephrine	• Phenylephrine is the drug of choice for Fundoscopy in adults to visualize the retina. • Phenylephrine eye drops are used to stimulate α_1 receptor on the radial muscles of the iris • Contraction of radial muscles of iris causes active mydriasis
Atropine	• Atropine is the drug of choice for Fundoscopy in children • Atropine blocks muscarinic M_3 receptors which paralyze the opposite muscles of radial muscles that are circular muscles • Normally circular muscles produce miosis and paralysis muscles leads to Passive mydriasis • In children M_3 receptors are overactive and 1% of ointment of Atropine is used for Fundoscopy in children

Nasal decongestants

00:06:02

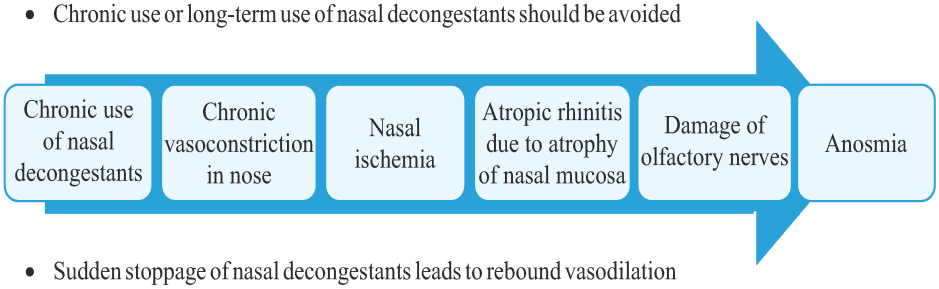
- Blood vessels are dilated in congestion causing plasma leak that manifests as rhinorrhea.
- Decongestants produce vasoconstriction in the nose and are used in the treatment of Rhinorrhea
- Types of nasal decongestants



- Phenylephrine produces vasoconstriction by α_1 receptor
- Zoline drugs produce vasoconstriction by stimulating α_{2B} receptors

Precautions to be taken while using nasal decongestants

- Chronic use or long-term use of nasal decongestants should be avoided



- Sudden stoppage of nasal decongestants leads to rebound vasodilation
  - Rebound Rhinorrhea: More plasma leaks leading to excessive Rhinorrhea
  - Rebound Rhinorrhea due to sudden stoppage of nasal decongestants is known as Rhinitis medicamentosa

Bronchodilators

00:12:10

- β_2 receptors on small bronchus cause bronchodilation.
- Hence bronchodilators are used in the treatment of Asthma
- Various drugs used in asthma are
  - Salbutamol
  - Formoterol
  - Terbutaline

Tocolytics

00:13:20

- Tocolytics are the drugs that relax the uterus.
- Tocolytics are drugs that reduce the contraction of the myometrium and delay or inhibit LABOR
  - Used in premature deliveries
- β_2 agonists showing tocolytic action
  - Ritodrine
  - Isoxsuprine
- Salbutamol being a bronchodilator has a tocolytic effect but it is not used as a tocolytic

β_3 agonist

00:15:25

Location of β_3 receptors

Adipose tissue	Bladder
• Causes lipolysis	• On bladder there is a detrusor muscle • Drugs relax detrusor muscle • Hence the urine will not pass out

Sibutramine	Merabegron	Vebegron
• Promotes lipolysis: Used as an anti-obesity drug • Banned due to its cardiotoxicity- Causes Arrhythmias, damage to mitral and tricuspid valve of the heart	• Acts on the bladder - Relaxes the detrusor muscles • Given in the treatment of Overactive bladder (symptoms of urinary incontinence)	• Acts like merabegron • New drug added into β_3 agonist

Indirectly and mixed-acting adrenergic drugs

00:18:10

Indirectly acting adrenergic drugs	Mixed acting adrenergic drugs

• They increase the release of catecholamines
• The drugs are
  ○ Modafinil
  ○ Amphetamine group
  ○ Tyramine
	• Cause release of catecholamines
	• Directly stimulate α and β receptors
	• These drugs are
	  ○ Mephentermine
	  ○ Ephedrine

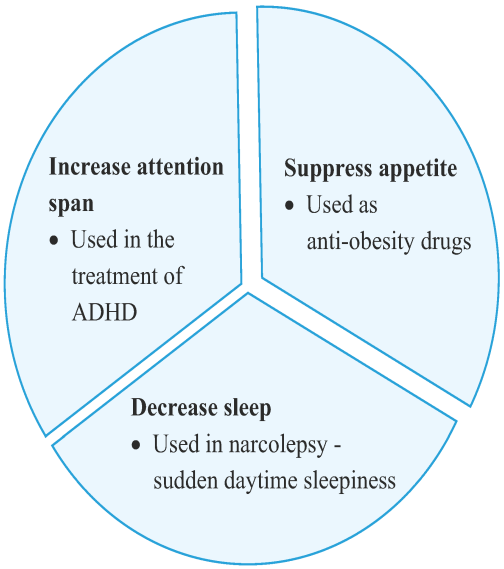
Example

- When amphetamine is taken on day one a very good effect will be shown
- But within a few days the effect of these indirect and mixed acting drugs will be reduced.
- As promotion of catecholamines is easy but the synthesis takes time.

- Indirectly acting and mixed drugs show rapid loss of effect because of depletion of stores of catecholamines inside the neurons
  - Loss of effect is known as Tolerance
  - This effect is also known as Rapid tolerance
- Rapid loss of effect or rapid tolerance is known as Tachyphylaxis
- These drugs have a very good Blood-brain barrier entry.

Effect of indirectly acting drugs and mixed acting drugs in the brain

- In the brain, sympathetic activity will increase



Modafinil 00:23:05

- It decreases sleep
- DOC for Daytime sleepiness
  - Occurs in narcolepsy
  - Occurs in OSA (obstructive sleep apnea)
    - → Apnea due to excess fat around the neck compressing the respiratory tract.
    - → Enantiomer of modafinil: AR-modafinil is used in OSA

Narcolepsy

Drugs approved for narcolepsy treatment

- **DOC: Modafinil** (sympathetic drug - reduces sleep)
- **Tiprolisant/Pitolisant**: H_3 (histamine) inverse agonist - cause wakefulness
- **Solriamfetol**: Increase norepinephrine and dopamine in brain - prevents sleepiness

Amphetamine

00:26:45

- Amphetamine's main action is in the brain due to its great ability to cross BBB and has less action in peripheral organs.

Uses

- Decreases appetite - anti obesity (but banned)
- Decreases sleep - narcolepsy (off-label use)
- Increases attention span - treatment of ADHD (Attention Deficit Hyperkinetic Disorder)

Drug of Abuse

- These are performance-enhancing drugs.
- Students abuse this drug
- Young people abuse these drugs while partying, hence they are called rave party drugs (required in low doses)- ECSTASY/crystal/ methamphetamine/MDMA.
- Abused by sportsmen (Dope test is done)

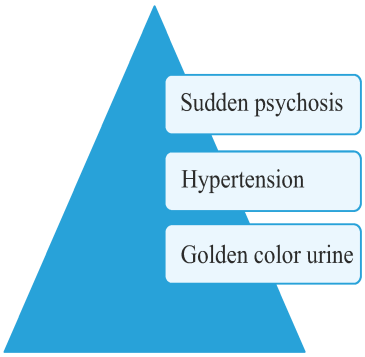
Side effects

- Seizures and psychosis
  - Pemoline is banned as it provokes seizures and psychosis
- Cardiotoxic
- Lead to hypertension and arrhythmias

Amphetamine poisoning

00:31:55

- Triad of Amphetamine poisoning



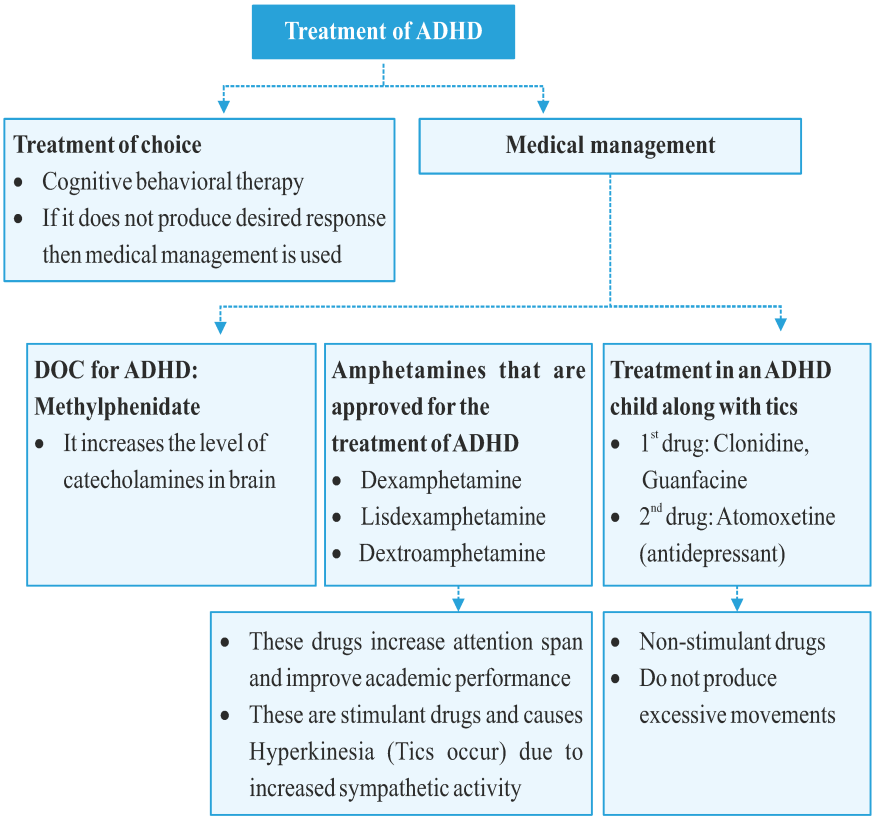
- **Treatment**

Ammonium chloride	• Drug of choice • Amphetamines are basic drugs • Ammonium chloride is acidic molecule that turns pH of urine acidic and causes forced acidic diuresis
Chlorpromazine	• Antipsychotic drug with α blocking action • Treats psychosis caused by amphetamines • α-blockers - produce vasodilation - decrease blood pressure • Treats hypertension • Used as symptomatic treatment

ADHD (Attention Deficit Hyperkinetic Disorder)

00:34:10

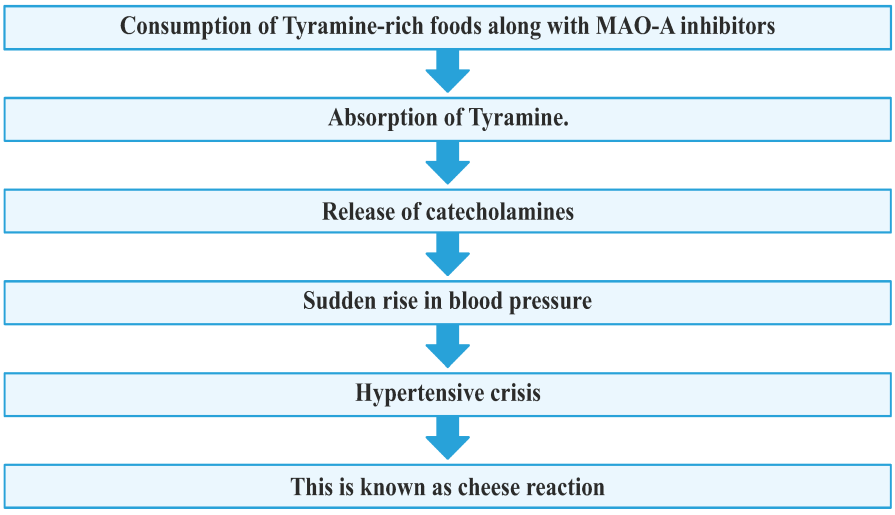
- ADHD is seen in small children
- These children have a poor attention span and often fail at school due to lack of attention/interest



Tyramine

00:38:44

- Tyramine is a food ingredient found in cheese, red wine, and meat.
- Normally tyramine does not get absorbed from GIT as it is degraded by the MAO-A enzyme



- **Treatment of Cheese reaction**
  - DOC: Phentolamine (α blocker)- Vasoconstriction does not occur and blood pressure does not increase

Ephedrine

00:41:58

- An old drug obtained from the plant - Ephedra vulgaris
- Uses
  - Nasal decongestant
  - Vasopressor - to treat hypotension in pregnancy
  - Asthma
- Ephedrine is modified to stereoisomers
  - Pseudoephedrine
    → Have less BBB entry compared to ephedrine
    → Used as nasal decongestant
  - Norephedrine (phenylpropanolamine)
    → More BBB entry
    → Increased risk of hemorrhagic stroke
    → Banned

Mephentermine (phentermine)

00:44:45

- Uses
  - As a vasopressor in the treatment of hypotension
  - Approved anti-obesity drug
    → Because of its sympathetic activity
    → Suppress appetite (anorexia)
    → Hence called an anorectic drug

Approved anti-obesity drug

00:45:40

Mephentermine + topiramate

- Mephentamine: Increases sympathetic activity and suppresses appetite
- Topiramate: Antiepileptic drug

Bupropion + Zonisamide

- Bupropion: Antidepressant
- Zonisamide: Antiepileptic drug

Bupropion + Naltrexone

- Naltrexone: Opioid antagonist

Liraglutide

- GLP-1 that suppresses appetite

Semaglutide

- GLP-1 that suppresses appetite

Orlistat, Cetilistat

- Oral lipase inhibitors
- Inhibits the breakdown of fats

Banned anti-obesity drugs

00:48:40

Amphetamine, Fenfluramine, Sibutramine

- All these drugs increase sympathetic activity by increasing amine levels in the brain
- Banned due to their cardiotoxic effect- causes cardiac valve damage

Rimonabant

- CB1 inverse agonist
  - CB1- cannabinoid receptor
  - Normally cannabinoids increase appetite
- Banned because it causes suicidal thoughts and depression

Lorcaserin

- Acts on serotonin 5HT2C receptors
- Suppress appetite
- It is banned because of its increasing risk of cancers
  - Colorectal cancer
  - Pancreatic cancer
- Recently banned drug

New anti-obesity drugs

00:50:55

Samidorphan

- Opioid receptor agonist
- Approved for treatment of olanzapine-induced obesity
  - Olanzapine blocks serotonin 5HT2C receptors
  - Increases appetite

Setmelanotide

- It is a melanocortin receptor agonist
- Suppress appetite
- Side effect: Increase in skin pigmentation

Effect of catecholamines on BP and Heart Rate

00:52:45

Blood pressure	Heart rate

• Mean arterial pressure (MAP) depends on diastolic blood pressure which in turn depends on the condition of the peripheral blood vessels
• If peripheral blood vessels constrict – BP is high
• If peripheral blood vessels dilate – BP is low
• On blood vessels
  ○ α_1 receptors causes vasoconstriction- Increase blood pressure
  ○ β_2 receptors cause vasodilation- Decrease blood pressure
	• Stimulation of β_1 receptors present on the SA node increases heart rate.
	• Direct heart rate depends on stimulation of β_1 receptors- Increases blood pressure
	• Indirect heart rate depends on blood pressure
	  ○ If peripheral blood pressure is high – reduced heart rate
	  ○ If peripheral blood pressure is low – increased heart rate
	  ○ It is the opposite of blood pressure
	• Brain, decreases HR to increased BP – called reflex bradycardia
	• Increase in HR to decreased BP – reflex tachycardia

Drug	BP	Direct heart rate	Indirect heart rate	Net heart rate
Norepinephrine (Acts on all receptors except β_2)	Increase – due to α_1 mediated vasoconstriction	Increase – by stimulating the β_1 receptor on the SA node	Reflex bradycardia – decrease HR	Bradycardia
Epinephrine (Acts on all receptors)	Biphasic change in BP – through α_1, produces vasoconstriction and increases BP – through β_2, produces vasodilation and decreases BP	Increases HR – by stimulating β_1 receptor	Negligible effect – due to existence of both vasoconstriction and vasodilation	Tachycardia – due to direct stimulation of heart
Isoprenaline/ Iso- proterenol (Acts on all β receptors)	Decreased - as it acts only on β_2 receptor	Increased HR – stimulation of β_1 receptors	Reflex tachycardia Increase in HR – due to vasodilation	Maximum tachycardia
Phenylephrine (Acts on α receptor)	Increases BP	No effect on direct HR	Reflex bradycardia Decreases HR	Bradycardia

Q. What is the net effect of norepinephrine on HR?
Ans. Bradycardia (because reflex predominates direct HR)

Q. Which drug causes bradycardia but is not directly acting on the heart?
Ans. Phenylephrine

Q. Why does norepinephrine in a normal heart produce bradycardia?
Ans. Because reflex nerves from brain predominate

- From the brain, the vagus nerve comes to the heart
- Release acetylcholine – produce bradycardia
  - Reflex bradycardia

Q. Does norepinephrine produce bradycardia in a transplanted/atropinized/denervated heart?
Ans. No – due to lack of vagal nerve innervation

- Norepinephrine in transplanted heart stimulates β_1 receptor
  - Only produces direct tachycardia
  - No reflex bradycardia seen
- The Vagus nerve produces acetylcholine
  - Acetylcholine is blocked by the drug - atropine
  - Hence reflex bradycardia does not happen in atropinized heart

Q. Which drug produces a biphasic change in BP?
Ans. Epinephrine

- Epinephrine shows biphasic change in BP
- Due to its action on α_1 receptor and β_2 receptors
- α_1 receptor stimulation
  - Vasoconstriction: Increase in BP
- β_2 receptor stimulation
  - Vasodilation: Decreases BP

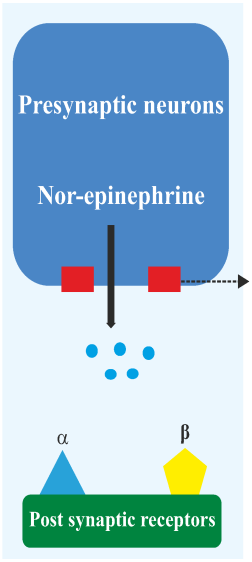
Q. What happens when an α blocker is given along with adrenaline?
Ans. BP decreases

- Vasoconstriction is inhibited by α-blocker
- Only β_2 mediated vasodilation occurs
- It is known as the vasomotor reversal of DALE (unopposed fall in BP)

18 ANTI-ADRENERGIC DRUGS

- Anti-adrenergic drugs reduce sympathetic activity in the body because the sympathetic nervous system is also known as the adrenergic nervous system
- They are also known as sympatholytic drugs

Classification of anti-adrenergic drugs



α_{2A} **agonists:** Inhibits the release of catecholamines

Stimulation of α_{2A} **receptors** present on presynaptic neurons inhibits presynaptic receptors leading to inhibition of the release of norepinephrine

α-blockers: Blocks postsynaptic α receptors

β-blockers: Blocks postsynaptic β receptors

α_{2A} agonist

00:02:47

- α_{2A}agonists inhibit the release of catecholamines like norepinephrine from presynaptic neurons

Clonidine

- Clonidine is the first drug developed for glaucoma, but was stopped as it was an oral drug.
- Now clonidine is modified into topical eye drops known as Apraclonidine and Brimonidine and used in the treatment of glaucoma.

Dexmedetomidine

- This is the most specific α_{2A} agonist.
- It reduces sympathetic discharge and produces sedation.
- Hence it's an IV drug used to produce sedation in ICU patients or as pre-anesthetic medication

Tizanidine

- Enters the brain and reduces sympathetic discharge and causes muscle relaxation
- It is also known as centrally acting muscle relaxant
- Given to patients with muscle rigidity

Guanfacine

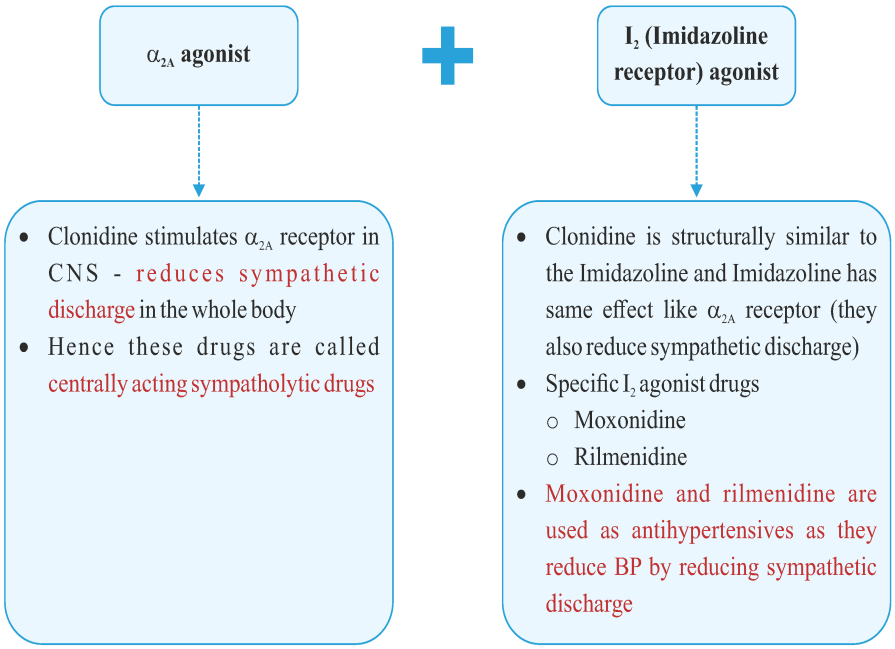
- It is longest acting drug
- Used same like clonidine
- Mainly used in treatment of Gilles de la Tourette syndrome (TIC disorder)
- Guanfacine produces calming effect and muscle relaxant effect

α Methyldopa

Clonidine

00:07:22

- **Mechanism of action**

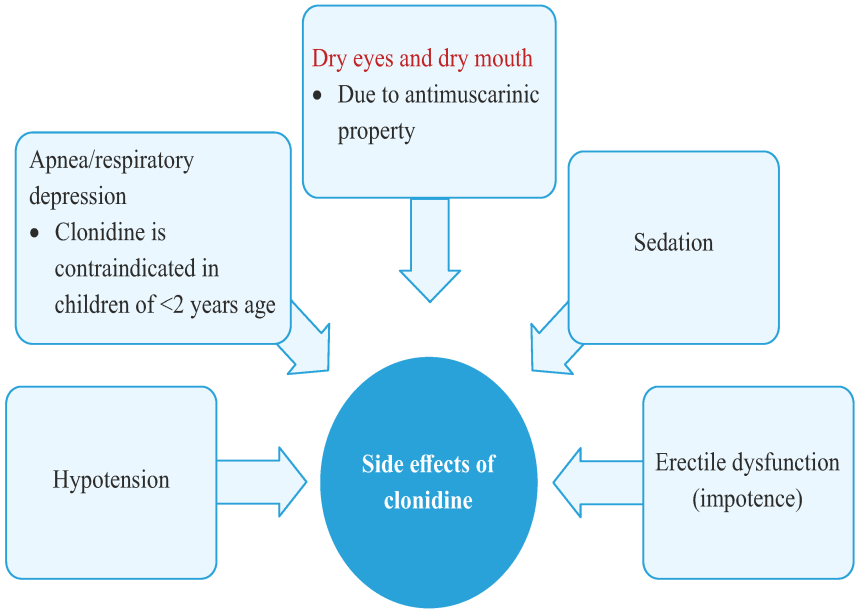


- **Properties of clonidine**
  - Clonidine in high doses is a non-specific drug
    - → It starts acting on receptors like α_{2B} receptor (postsynaptic receptor), thereby increasing blood pressure.
    - → It also starts blocking acetylcholine M_3 receptors (which have antimuscarinic properties) causing dry eyes and dry mouth
  - Route of administration: Oral, IV, Transdermal patches
  - Narrow therapeutic index drug: Low safety margin

Uses of clonidine	**Post menopausal hot flushes treatment** • Clonidine acts on the vasomotor area of the brain reducing the blood vessel tone and the risk of hot flushes • Drug of choice for postmenopausal hot flushes is hormone replacement therapy
	Hypertension treatment • Oral dose given for long-term use • IV dose in case of hypertensive emergency (hypertensive crisis)
	Diabetic diarrhea treatment • Clonidine stimulates α_{2A} receptor in neurons of the intestine and decreases intestinal secretions (Na^+ and Cl^- secretions are reduced) • Diabetic diarrhea occurs due to diabetic neuropathy which occurs because of excessive secretions through intestine
	Drug de-addiction • In case of smoking, alcoholism, and opioid overuse, withdrawal symptoms of any drug occur because of increased sympathetic activity. • Clonidine controls withdrawal symptoms by reducing sympathetic activity • Lofexidine (α_{2A} agonist) is used for withdrawal symptoms of opioids

	Epidural analgesia • Relieves pain by suppressing neuronal discharge
	Migraine prevention/prophylaxis
	ADHD treatment (Attention Deficit Hyperkinetic Disorder)
	Gilles de la Tourette syndrome (TIC disorder)

- Note: Mnemonic - PHD DEMAG
- Clonidine is used in the diagnosis of Pheochromocytoma
  - Sympathetic nerves from the brain go to the adrenal medulla
  - Under the influence of sympathetic nerves, the adrenal medulla releases epinephrine, norepinephrine, and various chemical molecules into the blood
  - Clonidine by inhibiting sympathetic neurons will decrease the production of catecholamines in the blood.
  - In pheochromocytoma (tumor of adrenal medulla), administration of clonidine causes no change/effect in the levels of epinephrine and norepinephrine



- Note: Mnemonic - HADSE

Q. Never stop clonidine suddenly in patients, why? PYQ: NEET PG 2023

Ans.

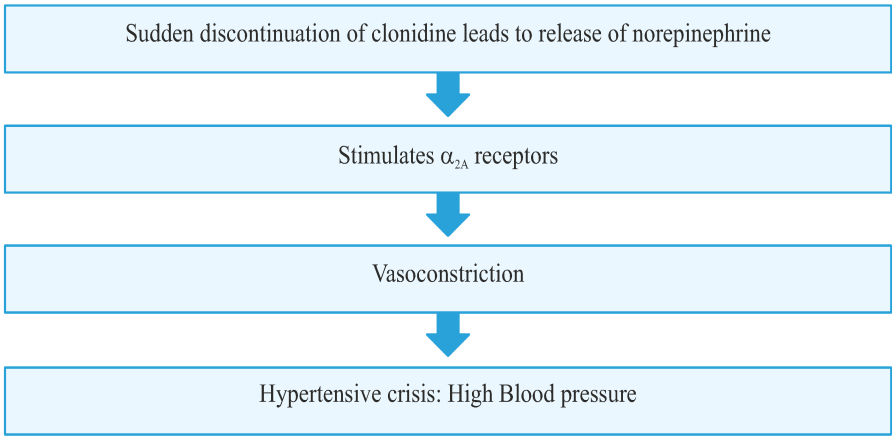
- A sudden discontinuation of clonidine causes a sudden rebound increase in blood pressure which may also lead to stroke and MI called hypertensive crisis

In the presynaptic receptors: Stimulation of α_{2A} leads to inhibition of norepinephrine.

↓

α_{2B} receptors on postsynaptic neurons increase in number and become super sensitive as they have not worked for a long duration.

↓



- **Management of hypertensive crisis**
  - Restart Clonidine immediately.
  - DOC for hypertensive crisis is Phentolamine (α blocker)

α Methyldopa

00:25:35

Mechanism of action

- α_{2A} agonist - decrease sympathetic activity

Uses

- In mothers α-Methyldopa is the drug of choice for chronic hypertension in pregnancy

Chronic hypertension in pregnancy

- A known hypertensive becomes pregnant.
- The drug of choice is α Methyldopa as it is the safest in pregnancy
- Labetalol is also used for the treatment of chronic hypertension in pregnancy

Pregnancy-induced hypertension

- A normal female, developing hypertension due to certain placental changes.
- The drug of choice is labetalol as it is the most effective

Side effects

- Depression
- Drug-induced lupus erythematosus
- Damage RBC (Warm Antibody Hemolytic Anemia)
  - α-Methyldopa attached to RBC, thus that RBC becomes antigenic after the attachment of α -Methyldopa
  - Antibodies (lgG) are produced against these RBCs and destroying them
  - It's a type of Type II Hypersensitivity
  - Coomb's test is used for diagnosis

Important Information

- The overall drug of choice for hypertension in pregnancy is Labetalol.

α-blockers and β-blockers

00:31:55

- β_1 receptors are present in the heart and increase the heart rate.
- α_1 and β_2 receptors are present in blood vessels
  - α_1 receptor causes vasoconstriction, increasing the blood pressure
  - β_2 receptors cause vasodilation, decreasing the blood pressure

α-blockers	β-blockers
Vasodilation activity	Vasoconstriction activity (except 3rd generation β blockers)
Causes reflex tachycardia	Causes Bradycardia
Causes vasodilation in the penile area (Corpus cavernosum) – causes penile erection (Priapism)	Causes vasoconstriction in the penile area (Corpus cavernosum) – cause erectile dysfunction – impotence
Reduces the risk of diabetes mellitus and dyslipidemia	Increases the risk of diabetes mellitus and dyslipidemia

- On the β cell of the pancreas, both α_2 and β_2 receptors are present
  - α receptors inhibit insulin secretion
    → α-blockers promote insulin secretion
    → Hence, it reduces the risk of diabetes mellitus
  - β receptors promote insulin secretion
    → β-blockers inhibit insulin secretion worsening diabetes mellitus

Important Information

- A special class of β blockers that do not produce vasoconstriction are 3rd generation β-blockers.

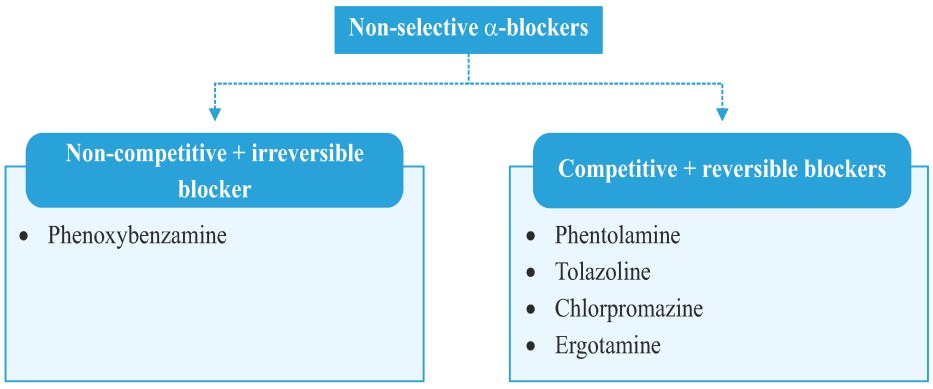
α-blockers classification

00:38:20

1. Non-selective α-blockers
2. Selective α_1-blockers
3. Selective α_2-blockers

Non-selective α-blockers

- Blocks both α_1 and α_2 receptors



Phenoxybenzamine

- IV drug
- Drug of choice for hypertension in pheochromocytoma
  - In pheochromocytoma, large amounts of epinephrine and norepinephrine is circulating.
  - First α-blocker is given then a β-blocker is added in the treatment of pheochromocytomas
  - The α receptors in blood vessels become free if β-blockers are given first.
    → Epinephrine and Norepinephrine stimulate α receptors leading to vasoconstriction and increasing blood pressure.
- Side effect
  - α blocking causes vasodilation leading to reflex tachycardia
  - Treated with β blocker - propranolol

Phentolamine

- Given IV in the diagnosis of pheochromocytoma
- Drug of choice for Cheese reaction
- Drug of choice for clonidine sudden stoppage (hypertensive emergency)
- Given as cavernosal injection
  - Used in the treatment of erectile dysfunction

Tolazoline

- Given as vasodilator during angiography procedure

Chlorpromazine

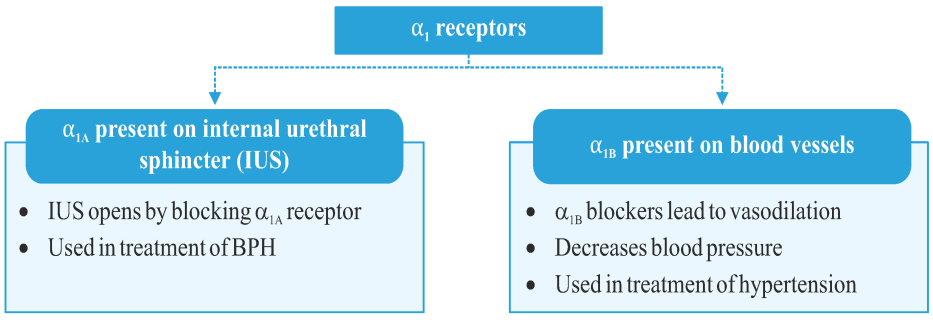
- Antipsychotic drug with α-blocking action

Ergotamine

- Serotonin agonistic action
  - Serotonin causes vasoconstriction in small blood vessels like in fingers
  - Causes side effect of ergotism- Ischemic necrosis of fingers
- α blocking action
  - Vasodilator in large vessels
- On hydrogenation, ergotamine is modified into Dihydroergotamine
  - It has more α-blocking property and less risk of ergotism

Selective α_1-blockers

00:49:47



α_1-blockers: Drugs blocking both α_{1A} and α_{1B} receptors

- Prazosin
- Terazosin
- Alfuzosin
- Doxazosin
  - α_1 - blockers are drug of choice for BPH with hypertension
  - Terazosin and Doxazosin can reduce prostate size in BPH

α_{1A}-blockers: Drugs that specifically block α_{1A} receptors

- Tamsulosin
- Silodosin
  - α_{1A} blockers are drug of choice for BPH without hypertension

Prazosin 00:54:20

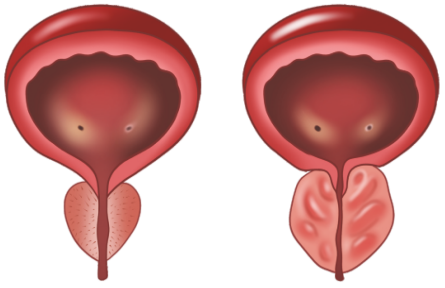
- **Uses**
  - BPH with hypertension
  - Scorpion sting
    → In Scorpion Sting, patients suffer from hypertension and pulmonary edema
  - Beneficial effect in diabetes mellitus and dyslipidemia
- **Side effects**

Postural hypotension (First Dose Effect)	• Occurs due to blockage of α_{1B} known as First Dose Effect (seen on the first day of starting Prazosin) • Treated by starting prazosin at a low dose and giving dose at bedtime • If postural hypotension is severe then treated with Midodrine (α_1 agonist)
Failure of ejaculation/retrograde ejaculation	• Due to blocking of α_{1A} receptors IUS sphincter opens • Behind IUS sphincter, there is an opening of seminal vesicles and their duct and opening of this sphincter causes retrograde ejaculation occurs
Floppy iris syndrome	• On iris α_{1A} receptors are present • α_{1A} normally produce mydriasis • Blocking α_{1A} receptors causes paralysis of iris

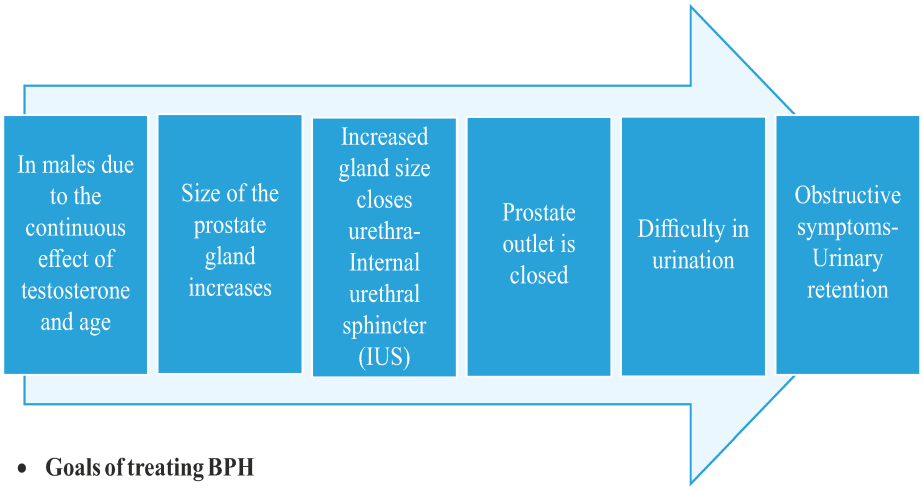
Important Information

- Postural hypotension is not seen in tamsulosin
- Retrograde ejaculation and Floppy iris syndrome are also seen with Tamsulosin as it is an α_{1A}-blocker.

Benign Prostate Hypertrophy (BPH) 01:01:25



Normal prostate Enlarged prostate



- **Goals of treating BPH**
  - Open urethral sphincter
  - Reduce the size of the prostate gland

Open IUs	• Relieve obstructive symptoms
	• Treatment of Dynamic component
	• Drug of choice: α_{1A}-blockers
	  ○ Tamsulosin
	  ○ Silodosin

Reduce prostate size	• Long-term goal
	• Treatment of static component
	• Drug of choice: 5α-reductase inhibitors
	  ○ Finasteride
	  ○ Dutasteride
	• Prostate is a testosterone-dependent gland
	• Active form of testosterone which increases the size of the prostate is DHT (Dihydrotestosterone)
	• DHT is responsible for secondary sexual characters in male like increase in prostate size and Alopecia/ baldness
	• Testosterone is converted to DHT by 5α-reductase enzyme
	• 5α-reductase inhibitors are also used in treating alopecia

Reduce prostate size	• These drugs show their actions after 6 months and are not effective
	• Surgery: Transurethral Resection of Prostate (TURP)
	  ○ Best treatment
	  ○ Remove prostate through urethra

Scorpion Sting 01:07:35

Clinical features

- Due to stimulation of α_1 receptors
  - Hypertension
  - Pulmonary edema
- Anaphylaxis
  - Hypotension/ shock
- Pain, muscle rigidity and seizures

Treatment

- Drug of choice: Antivenom
- Add drugs with antivenom to treat clinical features
- Prazosin: α_1-blocker
  - Hypertension
  - Pulmonary edema
- Epinephrine
  - In case of hypotension and anaphylaxis
- Diazepam
  - Muscle rigidity
  - Seizures
- Lignocaine
  - Pain

Selective α-2 blockers

01:10:30

- Yohimbine
  - Extracted from plants
  - Eat these plants for penile erection/increase libido
  - Not approved for use anywhere
- Idoxazon
- Antidepressants + α_2-blockers
  - Mirtazapine & Mianserin
  - Treatment of depression with sexual or erectile dysfunction
  - Improve penile erection

β Blockers

01:12:24

1st generation	2nd generation	3rd generation BB	
Non selective BB	Cardioselective BB	Additional property: Vasodilators	
Block: $\beta_1=\beta_2=\beta_3$	Block: $\beta_1>>>>\beta_2/\beta_3$	Non selective BB	Cardioselective BB
Maximum vasoconstriction	Less vasoconstriction	Block: $\beta_1=\beta_2=\beta_3$	Block: $\beta_1>>>>\beta_2/\beta_3$
Drugs • Propranolol • Pindolol • Penbutolol • Timolol • Nadolol • Sotalol	**Drugs** • Bisoprolol • Esmolol • Atenolol • Acebutolol • Metoprolol	**Drugs** • Carvedilol • Carteolol • Labetalol • Bucindolol	**Drugs** • Celiprolol • Nebivolol • Betaxolol

Additional Vasodilatory action of 3rd generation BB

Nitric oxide production	β_2 agonist action	Block calcium channel	Block α_1 receptor	Potassium channel opener
• Nebivolol • Nipradilol • Celiprolol	Celiprolol	• Betaxolol • Carvedilol	• Labetalol • Bucindolol • Carvedilol	Tilisolol

- K^+ channel opener moves K^+ ions outside muscle and makes muscle negative (Hyperpolarization)- Relaxation

Q. Which are Combined α and β blockers:

Ans.

- Labetalol
- Bucindolol
- Carvedilol

Q. Name three actions of carvedilol:

Ans.

- Calcium blocker
- α blocker
- Reduce oxidative stress (Antioxidant)

Q. Which is the longest acting β blocker:

Ans. Nadolol

Q. Which is the shortest-acting β blocker:

Ans. Esmolol

- t½: 10 mins
- Esterase in plasma degrades Esmolol rapidly

Q. Which is the most lipid-soluble β blocker:

Ans. Propranolol

- Maximum entry into brain- Used in conditions like migraine
- Side effects:
  - Seizures
  - Sleep: nightmares

Q. Which is the least lipid soluble β blocker?

Ans.

- Nadolol
- Atenolol
- Sotalol
- Acebutolol

Explanation

- They are lipid-insoluble or water-soluble drugs
- In the liver lipid-soluble drugs are converted to water-soluble molecules
- As least lipid-soluble drugs do not need any conversion, they do not enter liver
  - They are safe in liver diseases
- They are unchanged in the urine and are Contraindicated in renal failure
- Long-acting drugs
  - Longest: Nadolol

Q. Which is the most cardioselective soluble β blocker?
Ans. Nebivolol

Q. Which β blocker closes the potassium channel?
Ans. Sotalol

Explanation

- T wave is produced due to ventricular repolarization
- This is due to the movement of K^+ ions outside the heart, by the opening of the potassium channel
- Sotalol closes the potassium channel and inhibits ventricular repolarization
- Sotalol causes QT prolongation as T wave is delayed

Q. Which β blocker has antioxidant action?
Ans. Carvedilol>> Nebivolol

Q. Which β blocker increases HDL levels?
Ans. Bucindolol

Q. Which β blockers has cardioprotective action in CHF (Chronic Heart Failure)?
Ans.

- Bisoprolol
- Metoprolol succinate
- Carvedilol
- Nebivolol
  - Not approved in India

Important Information

- β blockers are contraindicated in Acute heart failure
- They decrease cardiac output, cause death
- In Acute heart failure, β agonist is given
  - Dobutamine
  - Norepinephrine

Special action of β blockers

01:30:50

ISA- Intrinsic Sympathomimetic Activity

• Generally, BB produce no sympathetic action but certain BBs produce little sympathetic action
  ○ Not complete antagonist or agonist
  ○ Partial agonists
• **Advantage:** Do not cause Bradycardia, due to sympathetic activity
• Safe in cardiovascular conditions
	Drugs
	• Celiprolol
	• Oxprenolol
	• Penbutolol
	• Acebutolol
	• Pindolol
	• Bopindolol

MSA- Membrane Stabilizing Action

• Membrane is destabilized due to the entry of sodium ions
• Some BB, block sodium channels
• Block sodium channels on heart
  ○ Atrial fibrillation- Suppress muscles on heart directly
  ○ Ventricular fibrillation
• Block sodium channels on neurons
  ○ Decrease nerve conduction
  ○ Local anesthetic action
  ○ Drugs- Lignocaine, Cocaine
  ○ Never given as topical eye drops
  → May lead to corneal anesthesia by acting on trigeminal nerve leading to loss of corneal reflex
	MSA BB drugs
	• Propranolol
	  ○ Maximum MSA
	• Metoprolol
	• Sotalol
	• Labetalol
	• Acebutolol
	• Pindolol
	  ○ These drugs are used in atrial and ventricular fibrillation
	  ○ Contraindicated in glaucoma

Uses of β Blockers

01:39:20

Block only β_1

- Prefer cardioselective BB
  - Atenolol
  - Metoprolol
  - Bisoprolol
  - Esmolol
- β_1 receptors are present in

Heart	JG cells of kidney
Actions • SA node: Increase HR • AV node: Increase conduction • Myocardium: increase cardiac output **Used in** • Tachycardia: reduce HR • Angina, MI: reduce oxygen demand	• β_1 releases Renin stimulating RASS and increasing BP • BB inhibit renin secretion from kidney • Treat hypertension ○ Not first line drugs in sole hypertension • BB are given in hypertension with angina, MI, Tachycardia
• HOCM (Hypertrophic Obstructive Cardiomyopathy) • Aortic dissection, Mitral valve prolapse	

Blocking both β_1 and β_2

- Prefer to give non selective BB
- Commonly used Propranolol
  - **DOC for:** 4P- HEAT

Prophylaxis of migraine

- Vasodilatory headache is cured by blocking β_2 and vasoconstriction

Pheochromocytoma with tachycardia

- First give α Blocker → BB

Performance anxiety

- Reduces tremors and heart rate

Portal hypertension

- Occurs in liver disease
- Portal vein pressure increases as liver is damaged
- Portal vein search for alternate route to reach Inferior vena cava
- Alternative route: Portocaval anastomosis
- It is connected by Left gastric vein
- Dilation: Esophageal varices
- Rupture leads to Hematemesis
  - DOC: IV Terlipressin
  - Earlier: IV Octreotide
- Maintenance: Oral Propranolol
  - Vasoconstriction of varices by blocking β_2 receptors
  - Prevention and long treatment

Hemangioma

- Dilated blood vessels on skin
- Cutaneous infantile hemangioma
- DOC: Propranolol and only drug approved

Essential tremors

- Occurs due to β_2 receptors
- Propranolol is a non selective BB

Akathisia

- Anxiety like situation due to use of antipsychotic drugs
- DOC: Propranolol

Thyroid storm/Thyrotoxicosis

- Occurs in hyperthyroidism due to sympathetic over activity
- Tremors and arrhythmias treated with propranolol
- Blocks β_1 and β_2 receptors
- Propranolol also inhibits peripheral T4 to T3 conversion

Adverse effects of β blockers

01:50:30

Due to β_1 blockage

- SA node: Bradycardia
- AV node blockage

Due to β_2 blockage

- β_2 receptors are present on smooth muscles, blood vessels, bronchus
- β_2 causes bronchodilation, vasodilation, insulin secretion
- Bronchospasm: Precipitate attack of Asthma/COPD
- Vasoconstriction: Peripheral Vascular Disease (PVD)
  - Coronary artery: Vasospastic angina
  - Fingers: Raynaud's disease
- Suppression of insulin secretion: Bad for diabetes and dyslipidemia patients

Non selective β blockers ($\beta_1 = \beta_2$)

- Propranolol blocks β_1 and β_2
- Contraindicated in
  - Bradycardia
  - AV node block
  - Asthma/COPD
  - PVD
  - Diabetes/ Dyslipidemia

Cardioselective BB

- Drugs: Atenolol, Metoprolol, Esmolol
- Mainly block $\beta_1 >>> \beta_2$
- Contraindicated in Bradycardia, AV node block
- Can be given in
  - Asthma/COPD
  - PVD
  - Diabetes/Dyslipidemia

Important Information

- β blockers are never combined with Verapamil and Diltiazem
  - Calcium channel blockers block SA, AV node on heart
  - Combination of BB and CCB cause marked bradycardia and heart block

Q. If a patient with Asthma/COPD comes comma the drugs used are:

Ans.

- Never give: Non-selective BB like Propranolol
- Can give with precaution: Cardioselective BB like Atenolol, Metoprolol
- DOC: CCB
  - Verapamil, Diltiazem
  - Do not cause asthma/COPD
  - Used as a replacement for BB

β-blocker toxicity (Overdose of Atenolol)

01:57:14

- Clinical features
  - Bradycardia
  - AV node block
- Antidote: Glucagon hormone
  - Has direct receptors on SA, AV node
  - Increases HR, AV node conduction
  - Physiological antagonist of BB

β-blocker in Diabetes mellitus

01:58:42

- β-blockers cause fluctuations in blood-glucose levels
  - Hyperglycemia
  - Hypoglycemia
  - Mask the symptoms of Hypoglycemia- Hypoglycemic unawareness

β blockers causing hyperglycemia

- Block β_2 on pancreas
- Inhibit insulin secretion

β blockers causing hypoglycemia

- Block β_2 in liver
- Inhibit glycogen breakdown
  - Glycogen in blood cause hyperglycemia in Fed state or obese
  - In starving or thin persons, lead to hypoglycemia

Hypoglycemic unawareness

- In diabetic patients, high dose of insulin causes hypoglycemia
- Sympathetic symptoms during hypoglycemic Emergency are:
  - Palpitations- β_1
  - Muscle tremors- β_2
  - Excessive sweating- Sympathetic cholinergic nerves
- Due to these unpleasant symptoms, patient eats and cures hypoglycemia
- Propranolol mask the symptoms of Hypoglycemia increasing its severity

Important Information

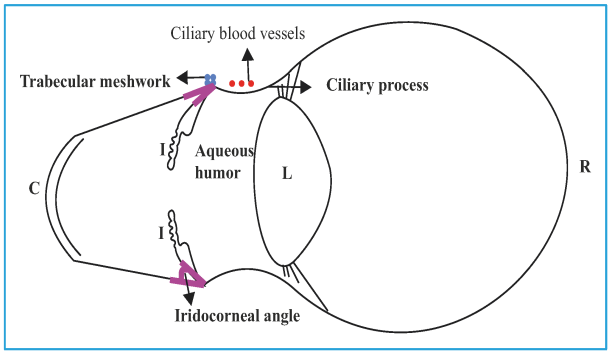
- Symptom of hypoglycemia which is not masked by Propranolol - Excessive sweating
  - Because sweating is not due to β receptor

19 GLAUCOMA

- Glaucoma is a condition in which optic nerve damage causes increased IOP (>21 mmHg) due to increased volume of aqueous humor.
- Ocular hypotensives are the drugs used to treat this condition.

Drainage of Aqueous humor

00:01:42



Ciliary blood vessels behind the ciliary process

↓

Blood filters

↓

Crosses ciliary epithelial cells

↓

Enters aqueous humor

↓

Crosses pupil

↓

Drains outside

↓

Trabecular meshwork
- Drains 90% aqueous humor
- Present between iris and cornea- Iridocorneal angle

Uveoscleral outflow
- 10% aqueous humor drains through this

- Primary open-angle glaucoma
  - This is mainly due to the reduced pore size of the trabecular meshwork.
- Angle-closure glaucoma
  - Closed iridocorneal angle due to mydriasis

Production of Aqueous humor

00:06:00

Receptors on Ciliary blood vessels	Receptors on Ciliary epithelial cells	Receptors on Uveoscleral/ episcleral veins
• **α 1 receptor** on ciliary blood vessels causes vasoconstriction and decreases aqueous production	• **α 2:** Decrease aqueous secretion • **β 2:** Increase aqueous secretion • **Carbonic anhydrase:** Increase aqueous secretion	• **PGF2 α:** Increases outflow PYQ: NEET PG 2022 • **α 2:** Increases outflow

- Glaucoma is treated by decreasing the production, decreasing the secretion, or increasing the outflow of aqueous humor. α-agonist drugs have all of the above actions.

+ Miotics	- Mydriatics
• They lead to thinning of the iris and open iridocorneal angle increasing trabecular outflow. • They are used in the treatment of the angle closure glaucoma.	• These are contraindicated in angle closure glaucoma as they close the iridocorneal angle and block trabecular meshwork • **Mydriatic drugs (Note: Mnemonic- ACTH)** o **A**tropine o **C**yclopentolate o **T**ropicamide o **H**omatropine o TCAs: shows the mydriatic effect

- Mechanism of action
  - Decrease aqueous production
  - Increases aqueous outflow/drainage
- Route of administration
  - Topical eye drops
  - Except for Acetazolamide, and mannitol which are DOC in Acute congestive glaucoma (IV)
- DOC for primary open-angle glaucoma & angle closure glaucoma
  PYQ: NEET PG 2019
  - PGF2 α agonist

PGF2 α agonist

00:14:20

Mechanism of action

Increase uveoscleral outflow

Route of administration

Given as topical eye drops

Drugs

- Ends with -prost
  PYQ: NEET PG 2021
  - Latanoprost
  - Bimatoprost- Approved for Hypotrichosis
  - Travoprost
  - Tafluprost
- DOC: Primary open-angle glaucoma & angle closure glaucoma
  PYQ: FMGE 2022

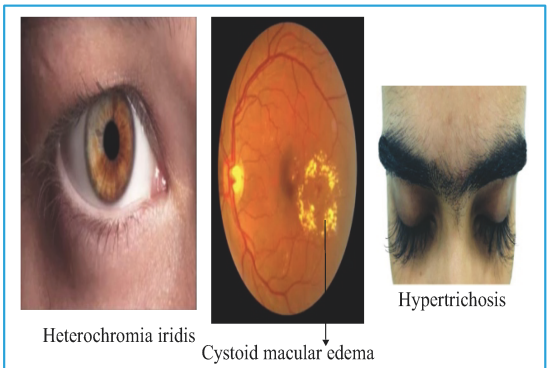
Side effects

Mnemonic: SOACHH

- **S**andy eyes
- **O**rbital fat atrophy
- **A**nterior uveitis
- **C**ystoid macular edema
- **H**eterochromia iridis
- **H**ypertrichosis/TrichomegaIy- Hair growth of eyelashes and eyebrows

Important Information PYQ: INICET 2022

PGF2 α agonists are contraindicated in Cystoid macular edema + Diabetes mellitus



β-blockers 00:21:25

Mechanism of action

These drugs block β_2 and reduce aqueous secretion from ciliary epithelium

Uses as topical eye drops PYQ: FMGE 2020

Non Selective β blockers	Cardio Selective β blockers

• Blocks β_1 and β_2 equally
• More effective
• Contraindicated in Asthma
• Drugs:
  ○ Timolol PYQ: FMGE 2022
  ○ Levobunolol: Longest acting
  ○ Carteolol
  ○ Metipranolol
	• Blocks β_1 >>>β_2
	• Safe in asthma
	• Drugs:
	  ○ Betaxolol: 2nd longest acting and has Retinoprotective effect
	  ○ Levobetaxolol

Side effects of β blockers as topical eye drops

- **Note: Mnemonic: ABCD**
- **A**llergic blepharoconjunctivitis
  - Maximum Allergy: Apraclonidine > Timolol
- **B**lepharospasm
- **C**orneal hypoesthesia
- **D**ry eyes

Miotics

00:27:12

Mechanism of action

- Stimulate M_3 receptor of ACh causing contraction of sphincter pupillae and miosis
- In glaucoma, miosis opens iridocorneal angle increasing the trabecular outflow

Drugs

PYQ: AIIMS 2019

- Pilocarpine: Stimulates M_3 agonist
  - Most commonly used
  - Used as eye drops: 0.5-4%
  - Available as implant: Ocusert
- Physostigmine: A carbamate increasing ACh
- Echothiophate: A organophosaphate increasing ACh

Side effects

- Ciliary muscle spasm (referred pain- brow pain, headache)
- Crying/ epiphora: Stimulates lacrimation, punctal stenosis of nasolacrimal duct
- Constrict pupil: Reduce vision/visual acuity
- Cataract: Caused by Echothiophate
- Retinal tears

α Agonist

00:32:54

- These drugs reduce aqueous production and increase uveoscleral outflow
- Drugs

Dipivefrin- α-1 + α-2 agonist

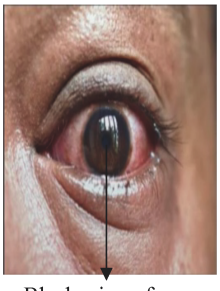
- A prodrug, which inside the eye is converted into Epinephrine (active form)
- **Side Effect of Dipivefrin:**
  - Hypertension
  - Angina/MI
  - Blackening of eye/dark eye
  - Conjunctival hyperemia (Red color eye)

α-2 Agonist

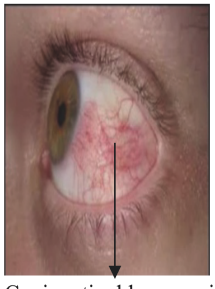
- **Drugs**
  - Apraclonidine: Short-acting
    → Only given for the treatment of IOP spike
  - Brimonidine: Long-acting
    → Used for long-term treatment of glaucoma
- **Side effects**
  - Allergic blepharoconjunctivitis
    → Max. Allergy: Apraclonidine
  - Lid retraction: Mostly with Apraclonidine
  - Respiratory depression/apnea- Most with Brimonidine

PYQ: NEET PG 2019

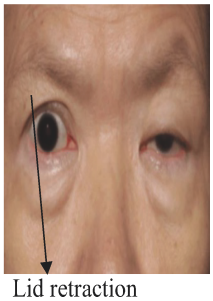
- Both the drugs are contraindicated in children <2 years
- Brimonidine: Safest anti-glaucoma drug in pregnancy (Category B)
- Rest all are: Category C



Blackening of eye



Conjunctival hyperemia



Lid retraction

Carbonic Anhydrase Inhibitors

00:42:48

Mechanism of action

Inhibit aqueous secretion through the ciliary epithelium

Types

Carbonic Anhydrase Inhibitors

Systemic (oral, IV)

- Acetazolamide
- Along with IV mannitol: DOC for acute congestive glaucoma

Topical eye drops

- Brinzolamide
- Dorzolamide: Add-on drug with PGF2 α agonist for open-angle and angle closure glaucoma

Contraindication

- Sulfa allergy
  - These drugs are sulfonamide derivatives

Sulfa allergy

- Leaky ciliary blood vessels lead to ciliary edema/ effusion
- The iridocorneal angle is closed as the iris is pushed forward due to increased thickness of ciliary process
- This causes Secondary angle closure glaucoma
- Antiepileptics that can cause secondary angle closure glaucoma are Topiramate and Zonisamide

New Drugs for Glaucoma

00:48:57

Netarsudil	Rho kinase inhibitor
	This leads to an increase in trabecular outflow
	Approved as Topical eye drops
	Used as an add-on drug with Latanoprost
	Side effect: Vortex Keratopathy (also caused by Amiodarone)
Omidenepag	PGE_2 agonist
	Available as eye ointment
	Increases both trabecular outflow & Uveoscleral outflow

Summary of management

00:51:20

Primary open-angle glaucoma & angle closure glaucoma

- DOC: PGF2 α agonist
  - Latanoprost, Bimatoprost
  - Add-ons: β blockers, α agonists, Carbonic anhydrase inhibitors

Acute congestive glaucoma

- IV Acetazolamide + IV mannitol
- If IOP falls, add PGF2 α agonist
- Definitive treatment: Iridotomy

Malignant Glaucoma

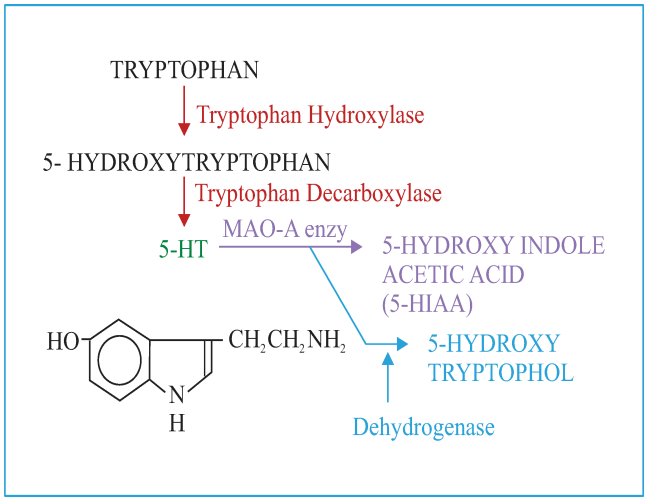
- A rare condition occurring after ocular surgery like Iridotomy
- Cycloplegics are used in the treatment of malignant glaucoma
  - Atropine
  - Cyclopentolate
  - Tropicamide
  - Homatropine

20 SEROTONIN

- Also called 5-hydroxytryptamine

Synthesis of Serotonin

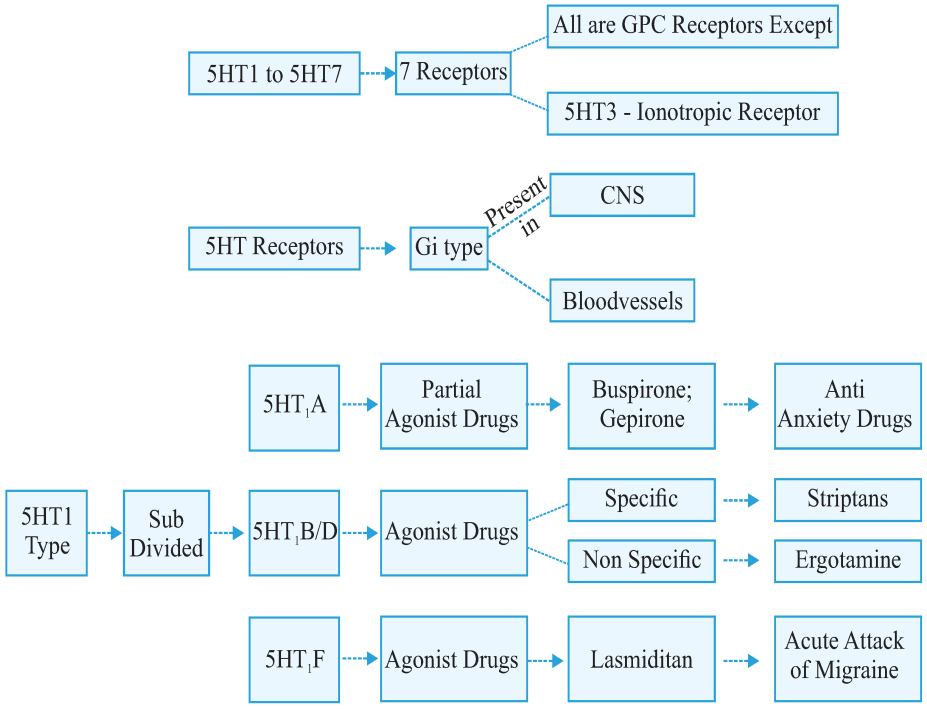
00:00:19



- Excess 5-hydroxy Indole acetic acid in urine: Marker of carcinoid tumor
- Telotristat - New drug
  - Inhibits tryptophan hydroxylase enzyme
  - Used in treatment of diarrhea in carcinoid syndrome
  - DOC in octreotide resistance

Serotonin Receptors

00:03:41



Serotonin Receptors

PYQ: NEET PG 2021

- 5HT1 to 5HT7
- All are GPCR
  - Except 5HT3
  - It is ionotropic receptor
    - → Among 7 receptors the major receptors are 5HT1-5HT4

5HT1 Receptor

00:04:55

- Gi type
- **Present on**
  - CNS neurons
  - Blood vessels
- **Sub types**
  - **5HT1A:** Partial agonist drugs are
    - → Buspirone
    - → Gepirone
    - → Used as anti-anxiety drugs
  - **5HT1B/1D:** Agonist drugs are
    - → Triptans: Sumatriptan (specific)
    - → Ergotamine - Nonspecific
    - → DOC for acute migraine attack (mainly triptans)

PYQ: NEET PG 2021

PYQ: FMGE 2020

  - **5HT1F:** Agonist drug is
    - → Lasmiditan
    - → New drug for acute attack of migraine

5HT1B/1D agonists

00:07:49

- Drugs include-Specific Agonist Drugs
  - **Sumatriptan**
    - → MC drug for acute migraine attack
    - → Can be given by many routes
      - Oral
      - Injection
      - Transdermal
      - Rectal
      - Sublingual
      - Nasal spray - Preferred if the patient has vomited during migraine
  - **Elitriptan:** Most effective drug for migraine
  - **Rizatriptan**
    - → Fastest action
    - → 2nd most effective drug for migraine
  - **Frovatriptan:** Longest acting drug
  - Almotriptan
  - **Naratriptan:** Has high oral bioavailability
  - **Zolmitriptan:** Can also be given as a nasal spray

Ergotamine --Nonspecific drug

00:10:39

- 5HT1B/1D agonist + Alpha blocker (causes vasodilation)
- Hydrogenation if ergotamine: Dihydro-ergotamine
  - Increases Alpha blocking action
  - Leads to more vasodilation
  - Less risk of ergotism

Mechanism in migraine

Trigeminal nucleus contains 5HT1B/1D receptors

↓

Release Inflammatory mediators like Serotonin, CGRP-2 (Calcitonin gene related peptide)

↓

Acts on blood vessels (arteries and veins)

↓

Leads to vasoconstriction

↓

Blood from the artery enters the vein

↓

Dilation of A-V shunt (contains 5HT1B/1D receptors)

- When 5HT1B/1D receptors are stimulated - It leads to vasoconstriction of Dilated A-V stunts
- Inhibits the release of Inflammatory mediators (Serotonin and CGRP-2)

Common side effects 00:15:09

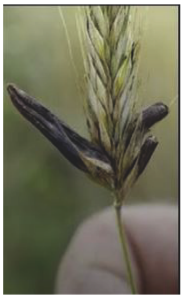
- Hypertension
- In the coronary artery, vasoconstriction causes vasospastic Angina/ MI
- **Erythromelalgia:** Redness and pain in fingers
- Raynaud's disease
- Dry gangrene of fingers (ischemic necrosis) - known as ergotism

To Remember: Triptans and ergotamine should be avoided in heart diseases

Ergotism

- Can be treated by nitroprusside (vasodilator)

Ergots 00:18:28



Crop with fungus

- Fungal product
- **Source:** Claviceps Purpura
  - Infests and damaged crops
  - In older times people who ingest these crops suffers from ergotism
  - Previously known St Antony's fire

St Antony's fire

- Ergot derivatives—3 Types Dopamine, oxytocin, Serotonin Agonists
  - **Dopamine agonist**
    - → **Drugs**
      - Bromocriptine
      - Cabergoline
      - Pergolide
      - Quinagolide
    - → **Uses**
      - Parkinson's disease
      - Prolactinoma treatment
  - **Serotonin agonist**
    - → Ergotamine and Dihydro-ergotamine
    - → Used in migraine treatment
  - **Oxytocin agonist**
    - → **Drugs**
      - Ergometrine (ergonovine)
      - Methylergometrine (methergine)
    - → Used to contract the uterus to control postpartum hemorrhage
    - → Contraindicated to induce labor - Risk of Fetal hypoxia
  - **Common side effects (Mnemonic: PAPER)**
    - → **P**ostural hypotension (bromocriptine)
    - → **A**bortion
    - → **P**sychosis or hallucinations
    - → **E**rgotism
    - → **R**aynaud's disease

- **Other ergot derivatives**
  - **LSD -** Potent hallucinogen
  - Ergotoxine (codergocrine)
    → Increases memory
    → Nootropic drug
    → Used in the treatment of Alzheimer's disease
- **Most potent side effect:** Inflammatory fibrosis 00:26:37
  - **Cardiac Valvular fibrosis**
    → Due to this pergolide is banned
    → Maximum seen with cabergoline
    → Not seen with Quinagolide
  - **Retroperitoneal fibrosis**
    → Methysergide was banned
  - Pleural fibrosis
  - Peritoneal fibrosis

CT scan of pulmonary and pleural fibrosis 00:27:54

- **Drugs causing pulmonary and pleural fibrosis (Mnemonic-BADNEST)**
  - **B**leomycin PYQ: INICET 2020
  - **A**miodarone PYQ: FMGE 2019
  - **D**oxycycline
  - **N**itrofurantoin
  - **E**rgots
  - **S**ulfonamide
  - **T**alc
- Doxycycline and Talc are also used in the treatment
  - **Pneumothorax:** Air accumulation between visceral and parietal pleura
  - By pleurodesis (joining visceral and parietal pleura)

Migraine 00:30:12

- Unilateral, pulsatile throbbing headache
- Occurs due to vasodilation.
- **Associated symptoms:** AURA
  - Nausea and vomiting
  - Photophobia
  - Phonophobia

Acute Migraine Treatment

- **Mild headache**
  - NSAIDs + caffeine
  - **NSAIDs examples**
    - → Paracetamol
    - → Naprosyn
    - → Aspirin
    - → Indomethacin

- **Moderate to severe headache**
  - DOC: Triptans
  - MC used triptan is sumatriptan
  - Never combine triptans and ergots
  - If combining gap of > 24 hours should be maintained
  - In cases where triptans are not used - Opioids can be given
    - → Injections of morphine or pethidine
    - → Nasal spray of butorphanol

- **AURA**
  - **D2 antagonists are used**
    - → Domperidone
    - → Metoclopramide
  - **Antipsychotics**
    - → Chlorpromazine
    - → Prochlorperazine

- **Migraine in pregnancy**
  - DOC is paracetamol
  - Other drugs
    - → NSAIDs
    - → Sumatriptan

Chronic Migraine

- Headache for > 15 days in a month
- Prophylaxis of chronic migraine (Mnemonic: BACTAM)
  - **Beta blockers**
    - → Propranolol (DOC) PYQ: FMGE 2021
    - → Others
      - Timolol
      - Metoprolol
    - → Avoided in asthma
  - **Antiepileptics** (safe in asthma)
    - → Valproate
    - → Topiramate
    - → Gabapentin
  - **Calcium channel blockers**
    - → Flunarizine and verapamil
    - → Safe in asthma

- **Tricyclic antidepressants**
  - → Amitriptyline
  - → Nortriptyline
- **Antiserotonin**
  - → Ketanserin
  - → Cyproheptadine
  - → Methysergide
- **MAO inhibitors:** Phenelzine
- **Miscellaneous Drugs**
  - → Clonidine
  - → Botulinum toxin

- **CGRP-2 antagonist:** New drug class 00:39:53
  - **GEPANTS (Mnemonic: RATUZO)**
    - → Blocks CGRP-2 receptor
    - → **R**imegepant
    - → **A**togepant
    - → **T**ilcagepant
    - → **U**brogepant
    - → **Z**avegepant - Given as nasal spray
    - → **O**lcegepant
    - → Given in acute migraine and Prophylaxis of migraine

  - **MABs: Monoclonal antibody**
    - → Erenumab -
      - First MAB approved for migraine
      - Blocks CGRP-2 directly
    - → Eptinezumab
    - → Fremanizumab
    - → Galcanezumab
    - → The remaining 3 blocks CGRP-2 receptor
    - → Only given for Prophylaxis of migraine

5HT2 Receptor 00:44:02

- **5HT2C receptor**
  - Present in Brain
  - Suppress appetite
  - **Lorcaserin**
    - → 5HT2C receptor agonist
    - → Approved as an anti-obesity drug
    - → Banned due to increased risk of cancer (mainly colorectal cancer)

- **5HT2 A/B/C antagonist**
  - **Antipsychotics**
    - → Olanzapine
    - → Clozapine PYQ: NEET PG 2020
    - → Side effects: Obesity (olanzapine)

- **5HT2 to 5HT4 antagonist:** Antiserotonin drugs
  - Ketanserin
  - Retanserin
  - Cyproheptadine
  - **Uses**
    - → Migraine prophylaxis
    - → Serotonin syndrome
    - → Promote weight gain (off label use)

5HT3 Receptors

00:47:50

- Ionotropic receptor
- **Present in**
  - **GIT**
    - → Increases motility
    - → Causes diarrhoea
  - **CTZ area in the brain**
    - → When stimulated it causes vomiting

5HT3 antagonists: SETRONS- Antimotility & antiemetics

- **Antimotility (GIT)**
  - Alosetron
  - Given for treatment of diarrhoea in IBS
  - Given only in females
  - Contraindicated in males
    - → Causes ischemia of the colon
    - → Damages large intestine

- **Antiemetics (CTZ)**
  - Ondansetron
  - Granisetron
  - Tropisetron
  - Ramosetron
  - Palonosetron
    - → Most potent
    - → Longest acting
    - → Requires less dose
    - → Even effective in delayed CINV
  - DOC to suppressants vomiting in
    - → Gastroenteritis
    - → Chemotherapy induced nausea and vomiting (CINV)
    - → Radiotherapy induced nausea and vomiting (RINV)
  - Not effective in motion sickness
  - **Side-effects**
    - → Constipation
    - → QT prolongation on ECG

5HT4 Receptors

00:54:43

- Present on GIT
- Increases GI motility (prokinetic)
  - Treatment of gastroparesis
  - LES closes - Treatment of GERD
- Increases intestinal motility: Treatment of constipation

Prokinetics

00:56:32

- **5HT4 receptor agonist (end with PRIDE)**
  - **Drugs include (Mnemonic: CMRIP)**
    - → **C**isapride - Banned (increasing QT interval, Torsade DE pointes) PYQ: NEET PG 2021
    - → **M**osapride
    - → **R**enzapride
    - → **I**topride
    - → **P**rucalopride
    - → Tegaserod - Banned

- **D2 antagonists**
  - Antiemetic + prokinetic
  - Domperidone
  - Levosulpiride

- **Drugs increasing Ach**
  - Neostigmine
  - Increases stomach and intestinal motility

- **Antibiotic** PYQ: NEET PG 2022
  - Erythromycin and clarithromycin
  - Stimulates motilin receptors in GIT

- **Metoclopramide:** Has 3 effects 01:00:05
  - 5HT4 receptor agonist - Prokinetic action
  - D2 antagonists - Antiemetic action
  - Increasing Ach - Prokinetic action
  - No setron like action present
  - **Side effects**
    - → Drug induced Parkinson's disease (muscle dystonia): Treated with benzhexol

Domperidone vs Metoclopramide

- **Domperidone**
  - Does not cross BBB
  - Doesn't cause Parkinson's disease or muscle dystonia

- **Metoclopramide**
  - Can cross BBB
  - Can cause Parkinson's disease or muscle dystonia

To Remember

- **5HT3 antagonist**
  - **In GIT -** Decreases motility
    → Side effect: Constipation
    → Used in treatment of diarrhea
  - **In CTZ -** Antiemetic action
- **5HT4 agonist**
  - **In GIT -** Increases motility
    → Side effect: Diarrhea
    → Used in the treatment of constipation
  - **In CTZ -** It causes nausea and vomiting

21 HISTAMINE

- Auto - Self; Coids - Acting.
- Self-acting molecules or self-acting hormones.
- **K/S:** Local hormones.
  - The cell releases molecules which act as autocrine or paracrine.

Classification of Autacoids

00:00:58

- Based on structure or by their chemical nature.

Amine	Lipids	Peptides	Gas
• Histamine • Serotonin (5 Hydroxy tryptamine)	Eicosanoids (Derived from eicosatetraenoic acid) • Prostaglandins • Leukotrienes • Lipoxins • PAF	• Angiotensin • Endothelin • Urotensin • Bradykinin • Natriuretic peptide	• Nitric oxide

Amine Autocoids

Histamine

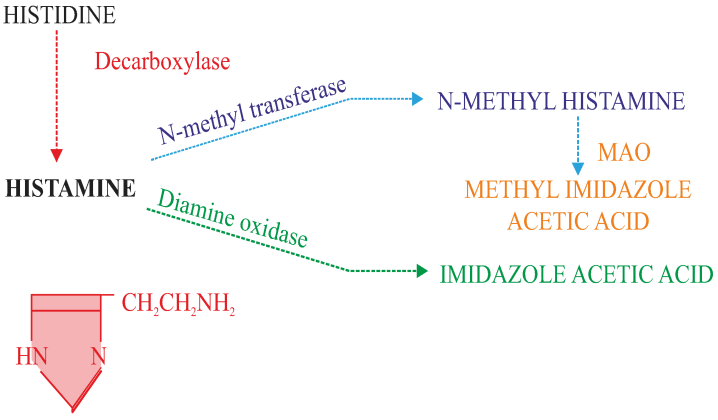


Fig. 11.1: Synthesis and degradation of histamine
MAO-Monoamine oxidase

- **Synthesis**
  - Histidine → Histamine (R-NH2)
  - Removal of carboxylic acid group.
  - Enzyme: Histamine decarboxylase.
- **Degradation:** MAO-A enzyme (Monoamine oxidase).
- **Receptors:** H1 to H4 receptors (All GPCR).

H1 Receptor

- Gq type of GPCR
- Activates phospholipase C which increases the levels of secondary messengers called IP_3/DAG.
- It causes responses in two locations;
  - **CNS (Neurons)**

→ Wakefulness
→ Increase in memory
→ Vomiting (Motion/sea/morning sickness)
→ Vertigo

- **Periphery (Mast cells/basophils)**
  → Allergic reactions (Type 1 HS)
    - Vasodilation
    - Pruritus
  → Intradermal histamine produces triple response
    - Redness → Wheal → Fare.

H1 Antagonists (Antihistamines)

- **1st Generation**
  - Cross BBB → Enters CNS.
  - Uses:
    → Sedation
    → Memory loss
    → Anti-vertigo
    → Antiemetic
  - These drugs also have anticholinergic actions, as they also block ACh receptors.
  - **C/I:**
    → Pilots, drivers, machinery operators (↑ risk of accidents)
    → Not to be taken during daytime, except Chlorpheneramine (Least sedative in 1st generation)
- **2nd Generation**
  - Do not cross BBB, except **Cetirizine** (The only 2nd generation antihistamic drug which crosses BBB and produce sedation)
  - They act only in the periphery.
  - Uses: Anti-allergic drug.

Note

- **Betahistine**
  - Partial agonist of H1 receptor
  - Brand name: Vertin
  - Used for treatment of: Vertigo (Any type)

1st Generation Antihistamines

- Classified as:
  - Highly sedative
  - Moderately sedative
  - Least sedative
- **Highly sedative**
  - Promethazine
    → Max sedation + Max anticholinergic + Max local anaesthetic (By blocking Na^+ channels).
    → Used in the treatment of drug induced parkinson's disease.
      - Also known as EPS/muscle dystonia.
  - Diphenhydramine
    → Transdermal patch
      - Arm, posterior auricular area, behind pinna.
    → For treatment of Motion sickness.

- Hydroxyzine
  - → Longest acting drug
  - → Active form: Cetirizine (2nd generation)
  - → It has maximum antipruritic effect.
  - → Given during nighttime as it causes sedation.
- Doxepin: Also classified under tricyclic antidepressants.
- Doxylamine (Along with Vitamin B6 - Pyridoxine)
  - → DOC: Morning sickness (Nausea/vomiting occurs during 1st trimester of pregnancy).

- **Moderately sedative**
  - Cyclizine, meclizine: Most effective drug for sea sickness >> motion sickness.
  - Cinnarizine
    - → Most effective drug for sea sickness >> motion sickness.
    - → Also, blocks calcium channels on vestibular nerves.
  - Cyproheptadine
    - → Antihistamine + Anti-serotonin action.
    - → Treatment of Migraine, increase appetite.
  - Pheneramine (Avil)
- **Least sedative**
  - Chlorpheniramine
    - → **Only 1st generation which** can be given in daytime.
  - Clemastin
  - Tirolidine

2nd Generation Antihistamines

- H1 receptor blocker + any 1 of the following property:
  - Do not cross BBB
  - Lack anticholinergic action
  - Additional anti-allergic action
- Only use is anti-allergic action.
- Mild symptoms of allergy
  - Rashes
  - Dry cough
  - Urticaria
  - Rhinitis
  - DOC: Antihistamines.
- Severe allergy (Anaphylaxis)
  - Patients may enter into shock due to hypotension.
  - DOC: Injection Epinephrine.
- Terfenadine and Astemizole
  - Substrate of CYP3A4 enzyme -
  - If CYP3A4 enzyme is inhibited by erythromycin or ketoconazole → ↑↑ Levels of Terfenadine and Astemizole → Toxicity. PYQ: NEET PG 2022
  - Toxicity can cause
    - → QT prolongation
    - → Torsades de pointes
  - Thus, these drugs combined with erythromycin or ketoconazole got banned
- Fexofenadine
  - Active form of terfenadine.
  - Adv: No QT prolongation, no sedation.
  - Commonly used brand name: Allegra.

- Cetirizine
  - Crosses BBB → Sedation.
  - Levo-cetirizine → Requires half dose → Less sedation.
- Loratadine → Des-loratadine: Most potent.
- Rupatadine → Additional antiplatelet action → Inhibits PAF.
- Ebastine, acrivastine, bilastine.
- Topical Drugs: Eye/nasal drops
  - 2nd generation antihistamines
  - Used for treatment of Allergic conjunctivitis or allergic rhinitis.
  - Mnemonic: ALOKA
    - → A - Azelastine - Max topical activity.
    - → L - Levocarbastine
    - → O - Olapatidine
    - → K - Ketotifen
    - → A - Alcaftadine

To Remember

- Additional mast cell stabilizing action
  - O - Olapatidine
  - K - Ketotifen

H2 Receptor

00:33:42

- Location: Stomach.
- Gs type of GPCR → Activates adrenal cyclase → ↑ cAMP → ↑↑ HCl (Acid production)

H2 Blockers

- Reduce HCl production in stomach.
- Drug name ends with -Tidine, except for Rufatidine which is an H1 blocker.
- Cimetidine
  - Bad drug
  - Least potent drug
  - Maximum CYP inhibition, which can lead to toxicity of other drugs.
    - → CYP enzyme produces testosterone and oestrogen
  - Maximum side effects
    - → ↓ Testosterone levels → Gynecomastia and impotence in males.
    - → ↓ Oestrogen levels → Menstrual irregularities.
    - → ↑ Prolactin → Galactorrhea (Blocks dopamine receptors in brain)
- Ranitidine: Less CYP inhibition.
- Famotidine: Noncompetetive H2 blocker.
- Roxatidine
- Nizatidine: No CYP inhibition.
- Lafutidine: Increase somatostatin → ↓↓ Gastrin production → ↓↓ Additional HCl production.

H3 Receptors

00:38:16

- Presynaptic autoreceptor
- Function: Inhibits own histamine release.
- Gi type of GPCR
- Tripolisant or Pitolisant: H3 inverse agonist.
  - Excessive histamine release → ↑↑ Wakefulness
  - New drug approved for narcolepsy (**DOC:** Modafinil).

H4 Receptors

00:40:38

- Gi type of GPCR
- Present on WBC → Responsible for chemotaxis
- No drug is available.

Clinical classification, disease and preparations of H_1 antihistaminic		
Drug	**Dose and route**	**Preparations**
HIGHLY SEDATIVE		
Diphenhydramine	25-50 mg oral	BENADRYL 25, 50 mg cap., 12.5 mg/5 ml syr.
Dimenhydrinate	25-50 mg oral	DRAMAMINE 16 mg/5 ml syr. 50 mg tab, GRAVOL 50 mg tab
Promethazine	25-50 mg oral, i.m. (1 mg/kg)	PHENEGRAN 10, 25 mg tab, 5mg/ml elixir, 25 mg/ml inj.
Hydroxyzine	25-50 mg oral, i.m.	ATARAX 10, 25 mg tab., 10 mg/5 ml syr, 6 mg/ml drops, 25 mg/ml inj.
MODERATELY SEDATIVE		
Pheniramine	20-50 mg oral, i.m.	AVIL 25 mg, 50 mg tab, 15 mg/5 ml syr, 22.5 mg/ml inj.
Cyproheptadine	4 mg oral	PRACTIN, CIPLACTIN 4 mg tab., 2 mg/5 ml syrup
Meclozine (Meclizine)	25 – 50 mg oral	In DILIGAN 12. 5 mg + niacin 50 mg tab In PREGNIDOXIN 25 mg + Ceffeine 20 mg tab
Cinnarizine	25 – 50 mg oral	STUGERON, VERTIGON 25 and 75 mg tab
MILD SEDATIVE		
Chlorpheniramine	2-4 mg (0.1 mg/kg) oral, i.m.	PIRITON, CADISTIN 4 mg tab
Dexchlorpheniramine	2 mg oral	POLARAMINE 2 mg tab, 0.5 mg/ 5 ml syr
Triprolidine	2.5 – 5 mg oral	ACTIDIL 2.5 mg tab
Clemastine	1-2 mg oral	TAVEGYL 1 mg tab., 0.5 mg/5 ml syr
SECOND GENERATION ANTIHISTAMINIC		
Fexofenadine	120-180 mg oral	ALLEGRA, ALTIVA, FEXO 120, 180 mg tab
Loratadine	10 mg oral	LORFAST, LORIDIN, LORMEG, 10 mg tab, 1 mg/ml susp.
Desloratadine	5 mg oral	DESLOR, LORDAY, NEOLORIDIN 5 mg tab
Cetirizine	10 mg oral	ALERID, CETZINE, ZIRTIN, TECZINE 5, 10 mg tab LEVOCET 5 mg tab, 2.5 mg/5 ml syr.
Azelastine	4 mg oral 0.28 mg intranasal	AZEP NASAL SPRAY 0.14 mg per puff nasal spray
Mizolastine	10 mg oral	ELINA 10 mg tab
Ebastine	10 mg oral	EBAST 10 mg tab
Rupatadine	10 mg oral	RUPAHIST 10 mg tab

22 LIPID AUTACOIDS

- They include
  - Prostaglandin
  - Leukotrienes
  - Lipoxins
  - Platelet activating factors
- These are synthesized from eicosatetraenoic acid
  - 20 carbons, 4 double bonds
  - Other name eicosatetraenoic acid- Arachidonic acid

Cell membrane is made of phospholipids
↓Inflammation
Functioning of Phospholipase A_2
↓
Breakdown of phospholipids
↓
Synthesis of arachidonic acid
↓
Cyclooxygenase enzyme (COX)
↓
Production of PG-G_2
↓
Further production of PG-H_2
↓
Production of PGI_2 (Endothelial cells), TXA_2 (Platelets), PG D_2, PG E_2, $PGF_{2\alpha}$ (Other cells)

- Prostaglandins have two double bonds.
- Arachidonic acid have four double bonds
- PGI_2
  - Other Name- Prostacyclin

Second pathway

Arachidonic acid
↓
5-Lipoxygenase enzyme (LOX)
↓
Production of leukotrienes like LT A_4 to LT B_4 to LT C_4/D_4

- Leukotrienes have three double bonds
  - Other Name- Slow reacting substance of anaphylaxis (SRS-A)
- LT B_4- Recruit eosinophiles
  - Responsible for type 1 hypersensitivity
    → Other Name- Anaphylaxis

Arachidonic acid

↓

Converts to lipoxins, platelet activating factor

Corticosteroids	• Block phospholipase A_2 enzyme • Reduce the production of arachidonic acid • Most effective antiinflammatory drug • Long term usage- Cushing syndrome
NSAIDs	• Blocks cyclooxygenase enzyme • Inhibits the conversion of arachidonic acid to prostaglandins
Zileuton	• Blocks 5 lipoxygenase enzyme • Recommended in asthma
Licofelone	• Blocks both COX and LOX enzyme • Use- Control inflammation in osteoarthritis
PAF antagonists	• Blocks platelet activating receptor • Drugs include ○ Apafant- Control inflammation in acute pancreatitis ○ Modifant

Various Types of Prostaglandins

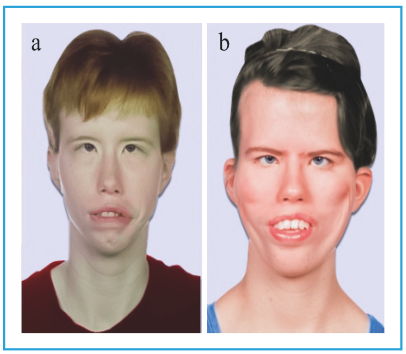
00:10:00

- First discovered in prostate gland

Prostaglandins	Synthetic preparation	Indications
PGE_1 • Mnemonic- GLAM	Misoprostol	• NSAID (Aspirin) induced peptic ulcer ○ Prostaglandins protect the stomach ○ Decrease HCl production, increase mucus production ○ DOC- PPIs • ROA- Oral • Medical abortions/MTP- Given in 1st trimester up to 63 days ○ ROA- Oral, sublingual, vaginal, buccal ○ Reason- Prostaglandin contract the uterus • Side effect- Diarrhea ○ Due to chloride secretion • Contraindication- Pregnancy ○ Abortion ○ Teratogenicity- Causes Mobius syndrome
	Alprostadil	• Causes vasodilation in penile blood vessel ○ Cavernosal injection ○ ROA- IV • Erectile dysfunction • Critical limb ischemia • Open ductus arteriosus

	Lubiprostone	• ROA- Oral • Other Name - Chloride secretor ○ In intestine • Treat constipation in IBS
	Gemeprost	• ROA- Vaginal • Medical abortion- 1st trimester

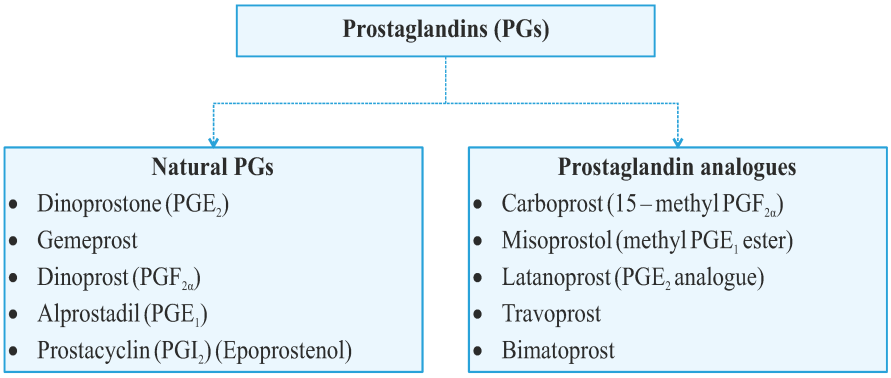
Mobius syndrome



- Malformation of 5th, 6th or 7th cranial nerves
- Teratogenic effect- Misoprostol
- Damage of 6th cranial nerve may also occur due to thalidomide
- Thalidomide- Causes Mobius syndrome, phocomelia

Prostaglandins	Synthetic preparation	Indications
PGE_2	Dinoprostone	• DOC for cervical ripening (Vaginal) • Induction of labor • Medical abortion (Vaginal cream)
$PGF_{2\alpha}$	Dinoprost	• IV drug • Medical abortion
	Carboprost PYQ: NEET PG 2023	• Medical abortion • Control postpartum hemorrhage ○ DOC- Oxytocin → Resistant cases- Carboprost • ROA- IM • Side effect- Asthma • Dose- 200 mcg IM ○ Maximum 8 Inj/day ○ Maximum dose- 2000 mcg/day
	Latanoprost Bimatoprost Travoprost Tafluprost	• ROA- Topical eye drops • DOC- Glaucoma ○ Increase Uveoscleral outflow ○ Both POAG, ACG
PGI_2 (Prostacyclin)	Treprostinil Iloprost Epoprostenol	• ROA- IV, inhalation ○ Not given orally • Causes vasodilation in lungs • Has anti platelet effect • DOC- Pulmonary artery hypertension • Anti platelet drug- During hemodialysis

- PGE_2, $F_{2\alpha}$- Medical abortions in 2nd trimester
- TXA_2
  - Opposite action of PGI_2
  - Causes
    → Vasoconstriction
    → Platelet aggregation or attachment on blood vessel
- Physiological antagonist- Drugs with opposite effect to each other
  - PGI_2 TXA_2



Medical Termination of Pregnancy

00:28:08

Class	Drug Name	Function
PGE_1	Misoprostol, Gemeprost	• Contract uterus • Expel the fetus out
PGE_2	Dinoprostone	
$PGF_{2\alpha}$	Dinoprost, carboprost	
Anti-progestin	Mifepristone (RU-486)	Kill fetus
Antifolate drug	Methotrexate	• Used in place of mifepristone • Kill fetus • WHO- Don't recommend this drug ○ Leads to incomplete abortion

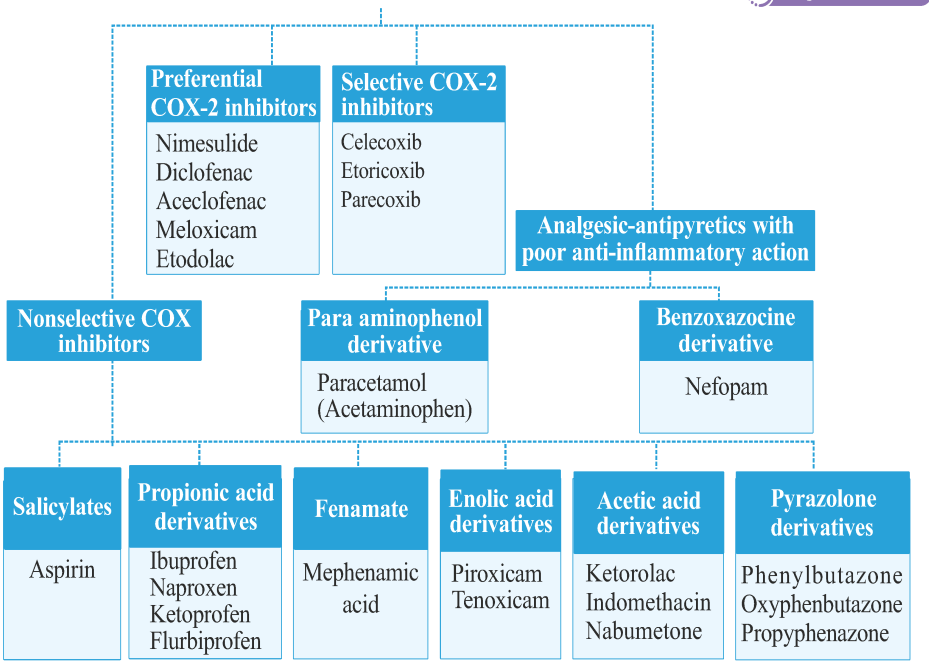
MTP Guidelines in India

- Day 1- Mifepristone
  - Dose: 200 mg
  - ROA- Oral
  - To kill the fetus
- Day 3- Misoprostol
  - Expel fetus by contracting the uterus
  - Given based on the gestation period.
    → Period of gestation- 49 days
      - Dose- 400 µg
      - ROA- Oral/Vaginal
    → Period of gestation- 63 days
      - Dose: 800 µg
      - ROA- Buccal/Vaginal/Sublingual
      - Not given orally in case of high doses

23 NSAIDs

Non-steroidal anti-inflammatory drugs/antipyretic-analgesics

PYQ: NEET PG 2021



MOA

- Inhibits COX enzyme.
  - Cyclooxygenase enzyme converts arachidonic acid into PG, TXA2
- Decreases the production of PG, TXA2

Type	Characteristic
COX-1	• Constitutive enzyme • Housekeeping: maintains normal body function
COX-2	• Inducible enzyme • Inflammation is the main function • Constitutive in brain, kidney, fetus

COX-3	• Present only in brain
	• Causes pain perception, fever
	• No role in inflammation
	• Paracetamol inhibits COX3
	  ○ Analgesic, antipyretic
	  ○ Poor anti-inflammatory effect

NSAID Drugs

00:04:46

- Irreversible COX inhibitor
  - Inhibits both COX-1 and COX-2
    → Aspirin

PYQ: FMGE 2023

- Non selective COX inhibitor
  - Inhibits both COX-1 and COX-2

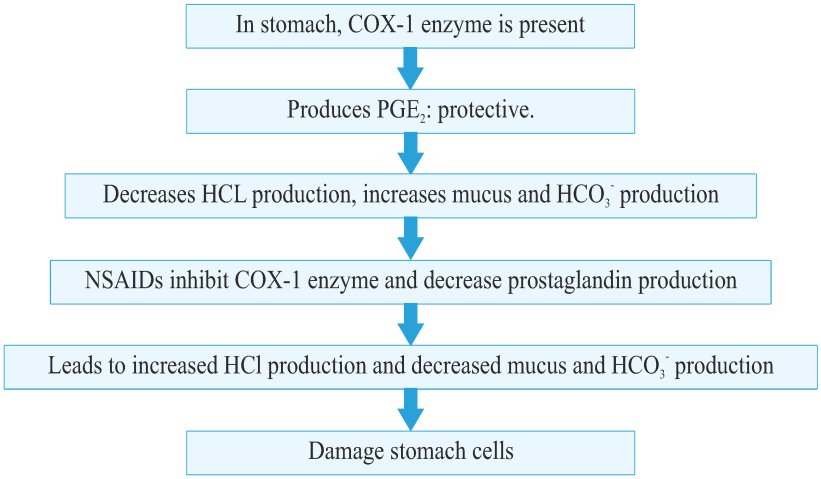
- Preferential COX-2 inhibitor
  - Inhibits COX-2 > COX-1
- Selective COX-2 inhibitor
  - Inhibits only COX-2
- Miscellaneous drugs
  - Analgesic + Antipyretic - Poor anti inflammatory
  - Don't act on COX-1 and COX-2

Common Uses of NSAIDs

- Analgesics
  - Given in all types of pain
    - → Not in neuropathic pain
  - In neuropathic pain: anti epileptics, local anaesthetics, TCAs
- Antipyretic
- Anti-inflammatory
  - Except paracetamol
- Anti platelet
  - For MI, stroke: Aspirin
- Closure of PDA: Indomethacin, Ibuprofen (DOC)
- Open ductus arteriosus: PGE_1 (Alprostadil)
- Tocolytic effect (relax uterus): Delay labour
- NSAIDs in pregnancy: Avoided
  - Causes premature closure of ductus arteriosus
  - Delay labour
- Safest in Pregnancy: Paracetamol
  - Has least effect
- NSAIDs are avoided in IBD
  - Ulcerative colitis and Crohn's disease
  - Safest Drug: Paracetamol

Common Side effects of NSAIDs

- Nausea, Vomiting: M/c
- Allergic reactions
  - Rashes, urticaria, pruritus (drug eruption)
  - Steven Johnson syndrome, anaphylaxis
- Peptic ulcer



- Aspirin causes gastric bleeding, gastritis
  - Maximum risk of peptic ulcer
- Less risk: selective COX-2 inhibitors (COXIBs)
  - Celecoxib
  - Paracetamol (COX-3)
- DOC for peptic ulcer: PPI (prazole)
  - Omeprazole, Pantoprazole
  - Misoprostol(PGE_1)
- NSAIDs are Nephrotoxic
- PGs cause vasodilation
  - Increases blood supply to kidney
- NSAIDs reduce renal blood flow, GFR
  - Causes acute tubular necrosis.
  - Causes oliguria
    - → Antidiuretic effect
      - Increased plasma volume
- Increased plasma volume causes increased Na^+/ K^+ levels
  - Leads to HTN, edema
  - Hyperkalemia
- Precipitates heart failure
  - Causes Papillary necrosis
- NSADs reduce the effect of diuretics(loop)
  - All together known as Analgesic Nephropathy
    - → Banned: Phenacetin

Aspirin

00:22:48

- Acetyl salicylic acid
- Irreversible COX Inhibitor
  - Hit & Run drug
  - Suicide inhibitor
- It acetylates COX enzyme by forming covalent bonds

Uses:

- Low dose(40-325mg): Anti platelet drug
  - Inhibits COX-1 enzyme
  - Decrease the production of TXA_2
  - Used in MI/ stroke
- Medium dose(700-800 mg)
  - Analgesic, Antipyretic
    - → Avoid the use of aspirin
    - → Increase the risk of "Reye's syndrome".
- High dose(3-5g)
  - Anti Inflammatory
  - DOC of Kawasaki disease, Osteoarthritis
  - Reduce the risk of colorectal cancer (familial adenomatous polyposis)
- Miscellaneous uses Aspirin
  - Niacin induced flushing
  - ACE inhibitor induced dry cough
  - Alzheimer's disease
    - → Not approved

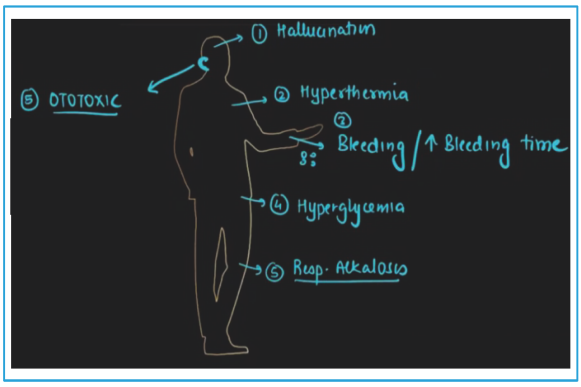
Precautions to Aspirin

- Avoided in Gout
  - Normal dose: <2g
    - → Increases uric acid levels
    - → Bad for gout
  - 2-5g: has variable effect
  - >5g: decreases uric acid
    - → Good for gout
    - → Dosage is toxic/ never used
- Avoided in Viral fever
  - Aspirin in viral infection leads to fulminant hepatic failure
    - → Known as Reye's syndrome
  - Safest Drug: Paracetamol
- Aspirin causing Asthma and Nasal polyp (Ethmoidal polyp)
  - Allergic symptoms
  - Known as Samtar's triad.
  - SAM- SAN (trick to remember)
    - → AS: Aspirin
    - → AS: Asthma
    - → NAS: Nasal polyp

Aspirin Toxicity

- Commonly available in household
  - Available as small pink tablets
- More risk in children

C/F:



- Brain: Hallucinations/ Psychosis
- Hyperthermia
  - Uncoupling of oxidative phosphorylation
- Leads to excessive bleeding
  - Due to anti platelet effect
  - Vitamin K Deficiency
- Causes hyperglycemia in normal dose
  - Hypoglycemia in toxic dose
- Ototoxic
  - Tinnitus, Vertigo
    - → Known as Salicylism
- Respiratory alkalosis followed by high anion gap metabolic acidosis

Treatment

- Antidote for Aspirin: Sodium Bicarbonate
  - Forced alkaline diuresis
- Severe poisoning: Hemodialysis
- VitK supplements are given
- All NSAIDs poisonings are treated the same way

Non-Selective COX inhibitors

00:40:38

- Reversible inhibitors of COX-1 & COX-2
- Indomethacin: DOC for Arthritis
  - OA, RA, Reactive Arthritis
  - Given in closure of PDA
- S/E: Sedation, seizures, pancreatitis, paradoxical headache
- Sulindac: Prodrug
- Ibuprofen: DOC for closure of PDA
  - Safe NSAID in children
  - Given for dental pain
  - S/E: Aseptic meningitis
- Ketoprofen, Flurbiprofen
  - Topical eye/ nasal drops
  - To treat conjunctivitis, Rhinitis
- Mefenemic acid
  - Blocks PG receptors
  - DOC for menstrual pain/ dysmenorrhea
  - S/E: Autoimmune hemolytic Anemia
- Phenylbutazone(sulfa): Banned
  - Most effective NSAID
  - Causes aplastic anemia/ agranulocytosis
  - Leads to bone marrow suppression
- Piroxicam/ Tenoxicam
  - Longest acting NSAID
  - Excreted in bile
    - → Reabsorbed in enterohepatic route
- Naproxen
  - 2nd most cardio safe
  - Safest: Aspirin
- Ketorolac
  - Given in IV/oral
  - Used in post operative analgesia
    - → DOC: Opioids

Preferential COX-2 inhibitor

00:48:11

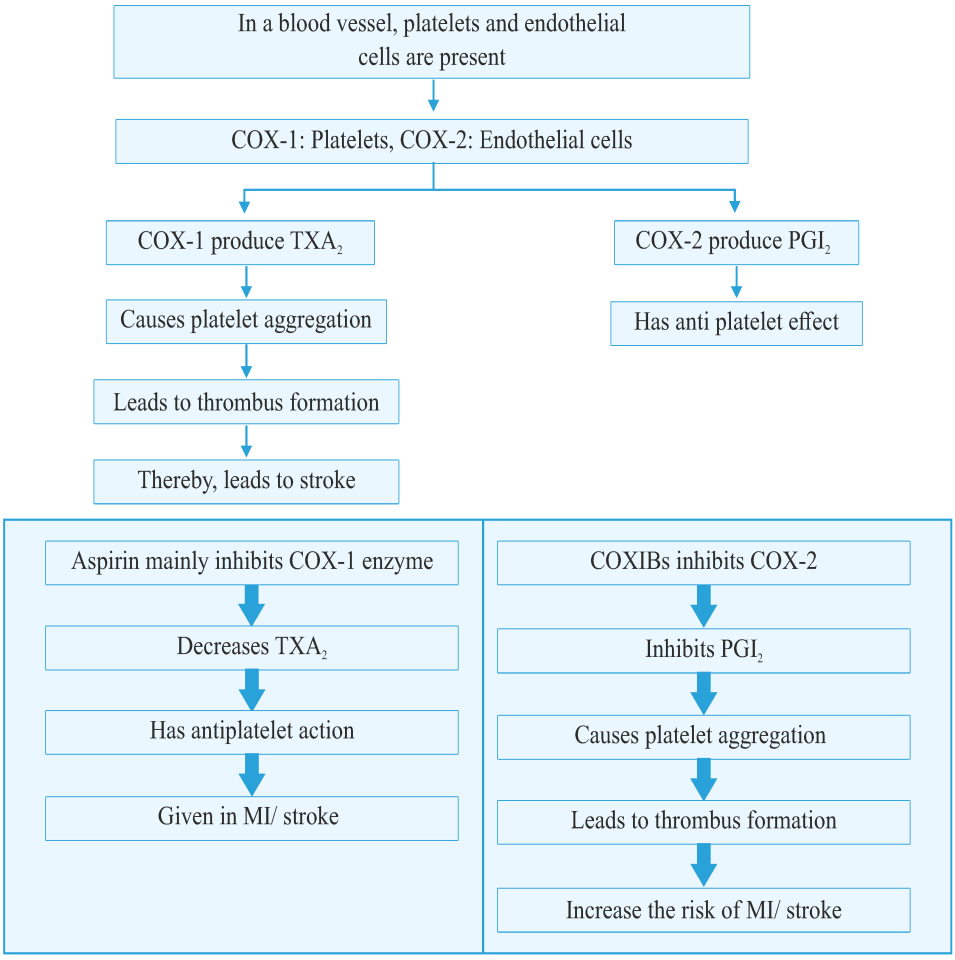
- Inhibits COX-2 > COX-1
- **Mnemonic: NMADE**
  - Nimesulide: Banned
    - → Highly hepatotoxic
    - → Causes Steven Johnson syndrome

- Meloxicam
- Aceclofenac
- Diclofenac (voveron, volini)
  - → Topical cream/ spray, Oral/IV
  - → Has good skin/ tissue penetration
  - → Accumulated in synovial joints
  - → Used in arthritis pain, sprain
  - → More hepatotoxic
- Etodolac

Selective COX-2 inhibitor

00:50:45

- Only inhibit COX-2 enzyme
- End with coxib
  - Rofecoxib
  - Valdecoxib
- Low risk of gastric/ peptic ulcer
- Increase the risk of MI/ stroke
  - By platelet aggregation
    - → Thromboembolism
  - So, these drugs got banned
- Approved drugs: Etoricoxib, Parecoxib, Celecoxib
  - Used in arthritis



Miscellaneous Drugs

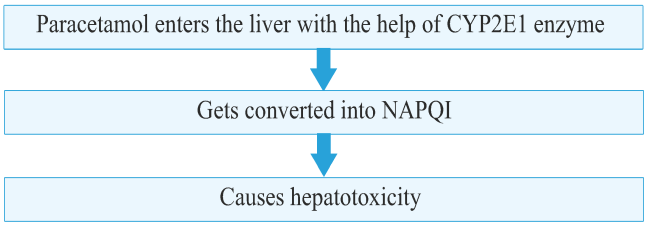
00:56:30

- Only Analgesic and Anti pyretic
- Poor anti-inflammatory effect
  - Don't act on COX-2
- Drugs: Paracetamol
  - Known as Acetaminophen
- Metamizole: Prodrug of paracetamol
- Nefopam: doesn't act on COX enzyme
  - SNDRI: seretonin norepinephrine dopamine reuptake inhibitor
  - Used to treat migraine, post anesthetic shivering
  - DOC: Pethidine

Paracetamol

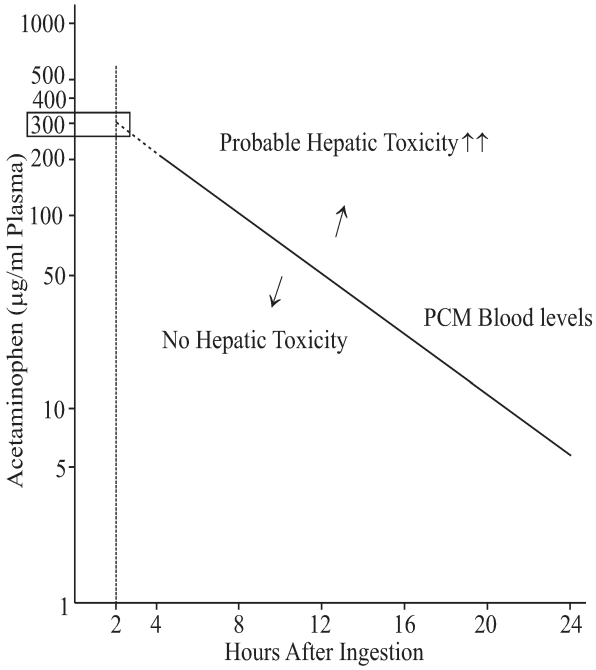
- Causes COX-3 inhibition
- Increase the level of endogenous cannabinoids
  - Stimulate TRP-V1 receptor.
- Safest in:
  - Children - No risk of Reye's syndrome
  - Renal failure

Paracetamol Toxicity



- NAPQI:
  - Toxic form of paracetamol in the liver
  - Gets excreted in urine with the help of Glutathione enzyme
- Pattern of liver damage due paracetamol- Zonal necrosis/ centrilobular necrosis with periportal sparing
- High risk of paracetamol hepatotoxicity in
  - Alcoholics
  - Smokers
  - Isoniazid
    - → By inducing CYP2E1 enzyme
- Antidote: N acetyl cysteine- DOC
  - Replenish glutathione stores in liver
- Methionine is also used for treatment

Graph



Semilogarithmic plot of plasma acetaminophen levels vs. time.

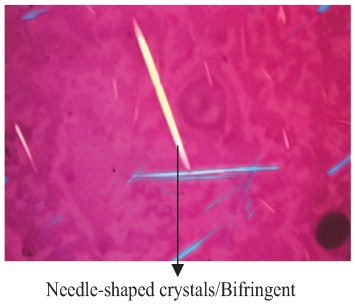
- Rumack Matthew Nomogram
  - A method to estimate paracetamol blood levels

24 GOUT

- Increase in uric acid levels in the blood.
- Other Name- Hyperuricemia

Increase in uric acid

- Deposits in tissues like joints (Tarsals) → Causes gout arthritis
- Deposits in tissues like ligaments below subcutaneous tissues - Tophi → Causes pruritis and pain
- Excreted through urine and deposited in the urinary tract → Formation of uric acid stones



Needle-shaped crystals/Bifringent

Management of Gout — Medicine — 00:02:25

Acute Gout

- Symptoms of arthritis
  - Pain
  - Redness
  - Swelling in joints

Treatment

- Anti-inflammatory drugs are used to reduce the inflammation of arthritis

Nephrotoxic drug

DOC- NSAIDS (All types) → Except Aspirin (Increases uric acid levels), Paracetamol (Poor anti-inflammatory effect)

↓ **Resistant to NSAIDS**

Colchicine

↓ **Resistant**

Renal safe drugs

Corticosteroids → **Avoid orally-** Leads to Cushing syndrome; **ROA-** Intra articular injections

Chronic Gout

PYQ: AIIMS 2020

- Persistent increase in uric acid levels
- Aim- To reduce the blood uric acid levels
- Drugs

PYQ: FMGE 2023

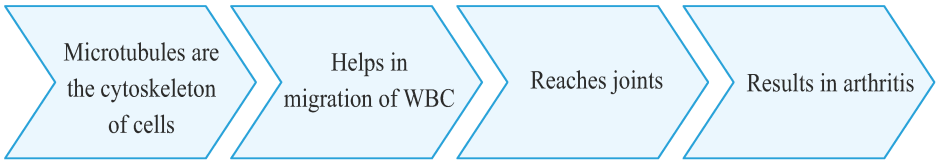
  - Xanthine oxidase inhibitors
  - Uric acid oxidase enzyme
  - Uricosuric agents

Colchicine 00:06:35

- Other Name - Spindle poison

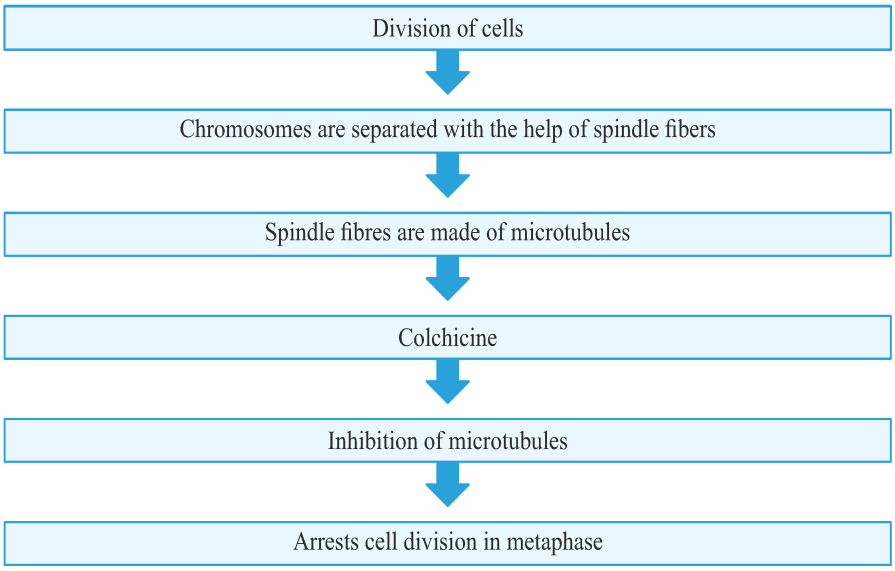
MOA

- Microtubule inhibitor



Uses

- In acute attack of gout
- Familial Mediterranean fever
- DOC for karyotyping



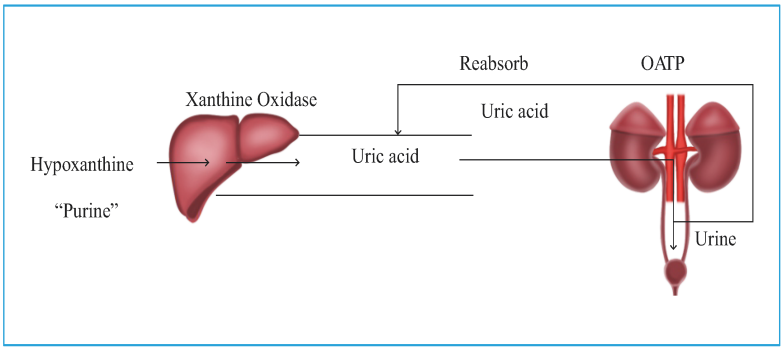
Side Effects

- GIT ulcers → Reduced absorption of food → Diarrhoea
- Bone marrow suppression

Drugs for Chronic Gout

- Reduce blood uric acid level

Production of Uric Acid



Xanthine oxidase Inhibitors	• Drugs ○ Allopurinol- DOC ○ Oxipurinol ○ Febuxostat → Recommended in allergic cases
Uric acid oxidase enzyme	• Degrade the uric acid in the blood into a harmless molecule ○ Known as allantoin • Drugs ○ Pegloticase PYQ: NEET PG 2020 ○ Rasburicase • Recommended in allopurinol-resistant cases
Uricosuric agents	• Increase uric acid excretion by blocking the OATP cotransporter • Drugs ○ Probenecid PYQ: FMGE 2023 ○ Benzbromarone ○ Sulfinpyrazone ○ Lesinurad • Rarely used

Xanthine Oxidase Inhibitors 00:16:42

Mechanism of Action

Blocks xanthine oxidase enzyme

↓

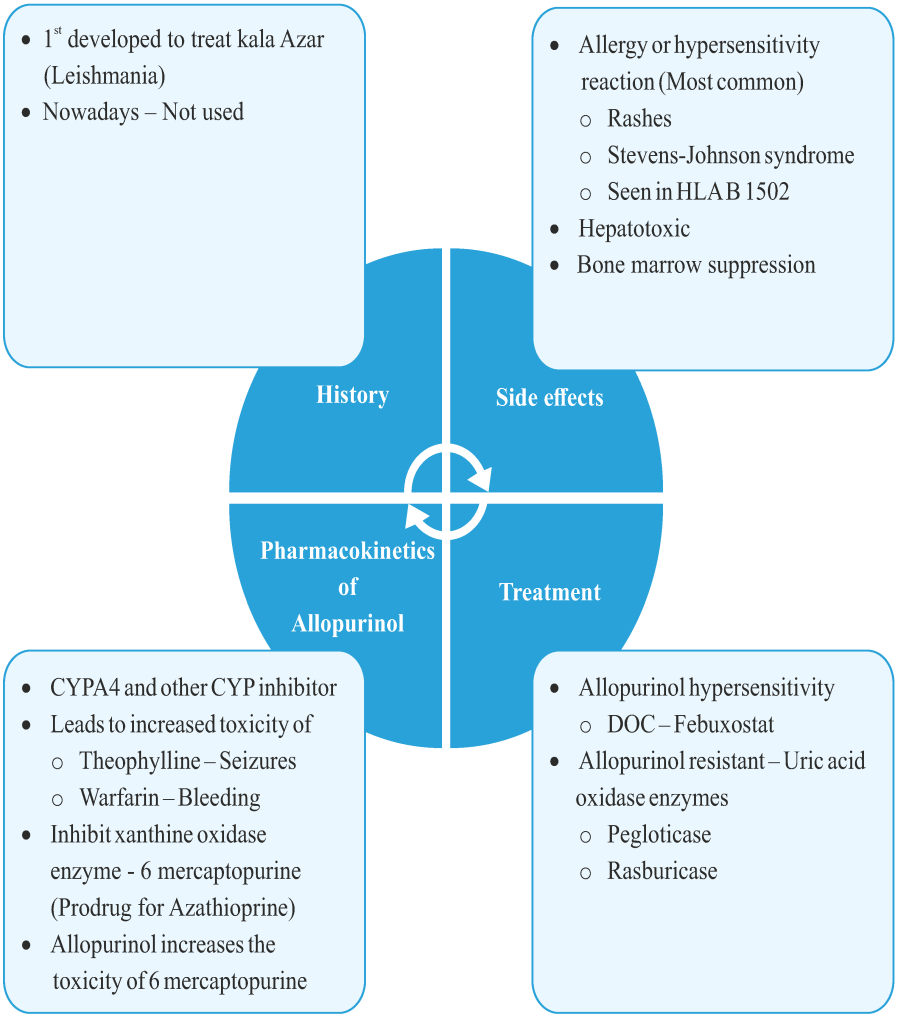
Inhibits the conversion of hypoxanthine to uric acid in liver

- Oxypurinol- Active form of allopurinol PYQ: NEET PG 2023
  - Other Name - Alloxanthine
- Allopurinol, oxypurinol- Competitive inhibitor of xanthine oxidase enzyme
- Febuxostat- Noncompetitive inhibitor of xanthine oxidase enzyme
- Allopurinol- DOC for chronic gout

Causes of Chronic Gout

- Renal failure/CKD
- Tumour lysis syndrome (Treatment of tumor with anti-cancer drugs leads to formation of purines like hypoxanthine goes to the liver to produce uric acid)
- Drug-induced gout

Allopurinol 00:20:27

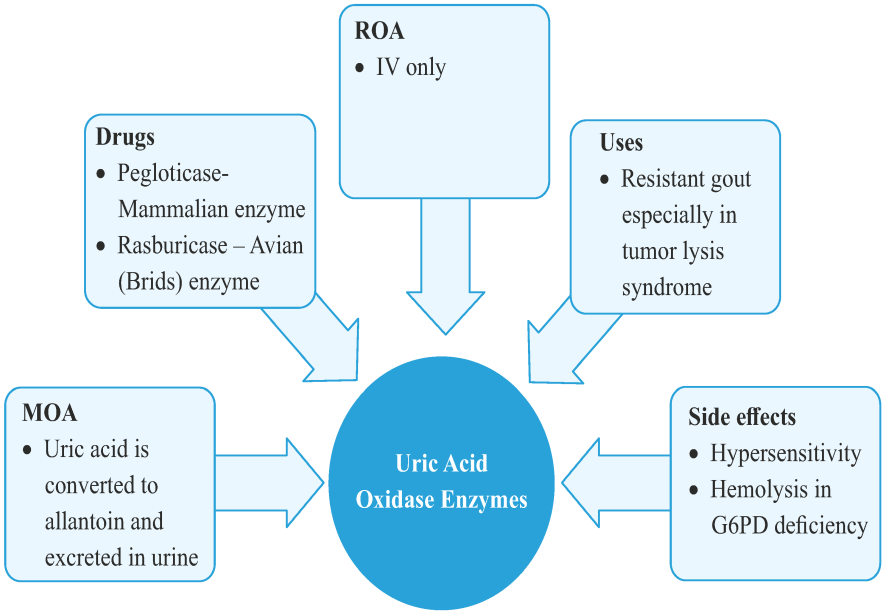


Important Information

- **Precaution-** 6 Mercaptopurine + Allopurinol: Reduces the dose of 6 Mercaptopurine by 75%

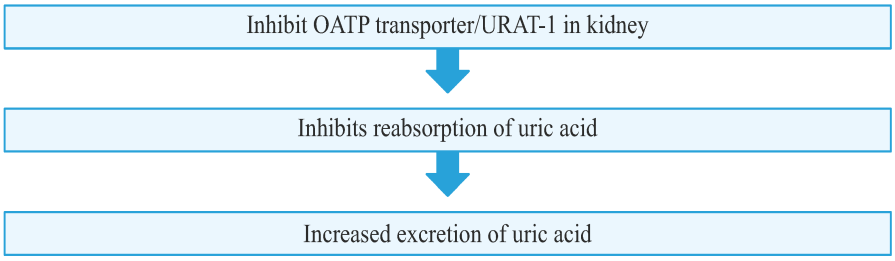
Uric Acid Oxidase Enzymes

00:26:33

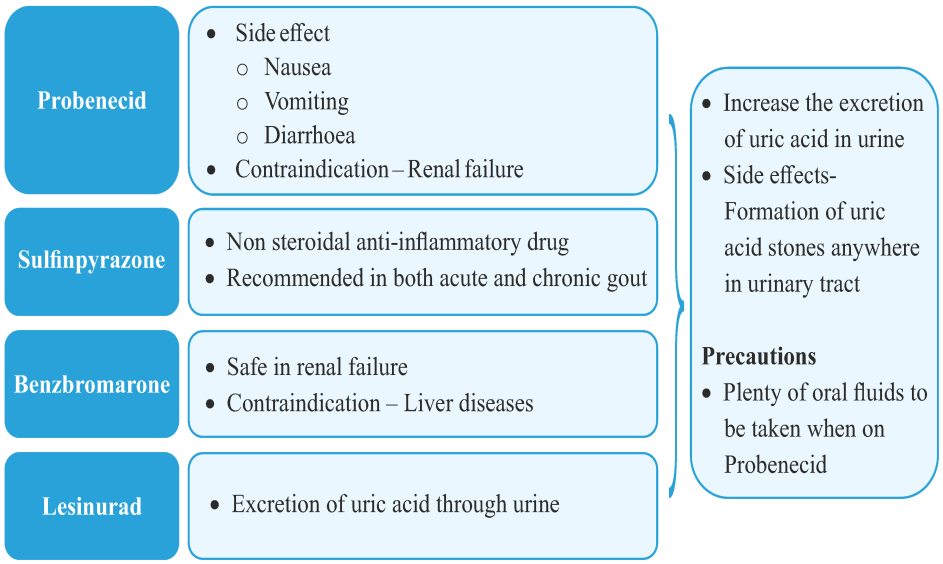


Uricosuric Agents

00:29:00



- OATP- Organic anion transport protein
- URAT 1- Uric acid transporter



Drugs causing Gout	Drugs Beneficial In Gout
• Mnemonic – **PAINED** ○ **P** – Pyrazinamide ○ **A** -Aspirin (Normal dose <2 gms) ○ **I** – Immunosuppressive drugs- Cyclosporine ○ **N** – Niacin ○ **E** – Ethambutol ○ **D** – Diuretic like loop diuretics, thiazides	• Mnemonic – **FALSe** • **F** - Fenofibrate • **A** - Aspirin in toxic dose >5 gm • **L** - Losartan • **Se** - Statins (Pravastatin, rosuvastatin)

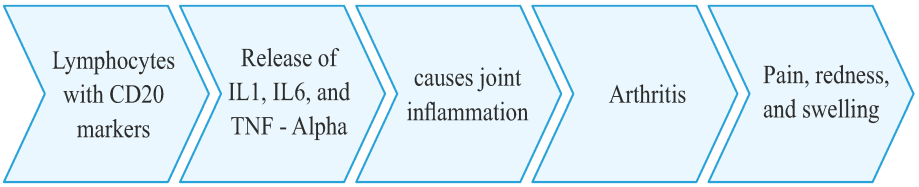
- Treatment for drug-induced gout- Continue the drug + Allopurinol.

Important Information

- Aspirin in normal dose <2gms- Bad for gout
- Aspirin in toxic dose >5gms- Good for gout
- Niacin reduces lipid levels- Bad for gout
- Fenofibrate reduces lipid levels- Good for gout

25 RHEUMATOID ARTHRITIS

- Rheumatoid arthritis is a Type 3 and 4 hypersensitivity disease
  - Uncontrolled and unwanted inflammation → Synovial joint destruction
- Most common joints involved: MCP and ICP
- Most common in a middle-aged female with a history of morning stiffness.



Drugs for Rheumatoid Arthritis

00:02:21

Acute arthritis

- Symptomatic treatment with anti-inflammatory drugs

DOC: NSAIDS

- All except paracetamol (poor anti-inflammatory action)
- Piroxicam
- Indomethacin
- Aspirin
- Diclofenac
- COXIBS (Celecoxib, Rofecoxib)

Resistant to NSAIDS: Corticosteroids

- Oral corticosteroids are avoided to prevent Cushing's syndrome.
- Intra-articular injection (Prednisolone, Triamcinolone)
- Advantages over NSAIDS
  - Not nephrotoxic
  - Reduced joint destruction

Long term definitive treatment – Retard joint destruction

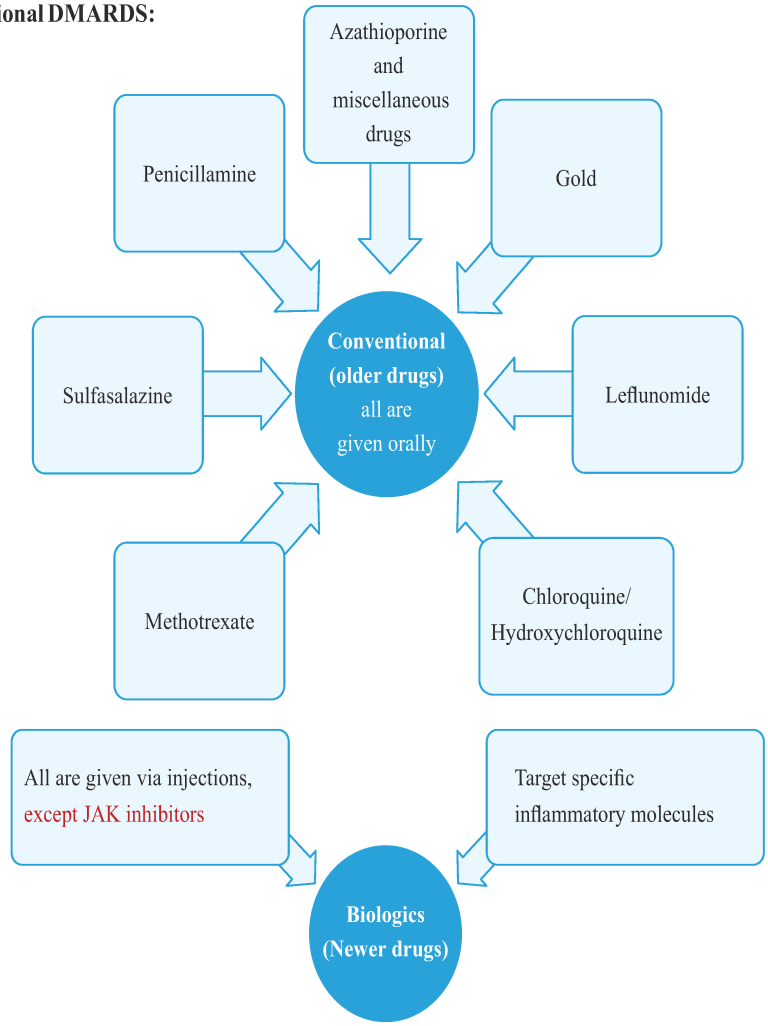
- DMARD – Disease-modifying antirheumatic drugs/ SAARD – slow-acting antirheumatic drugs
- Action begins after 1 month of using medications
- Not recommended for acute arthritis
- Bridge therapy – Start a patient's therapy with a corticosteroid and maintain the patient on DMARD.

DMARDS

00:07:15

1. Conventional (Older drugs) →Oral
2. Biologics(Newer drugs) →Mostly inj

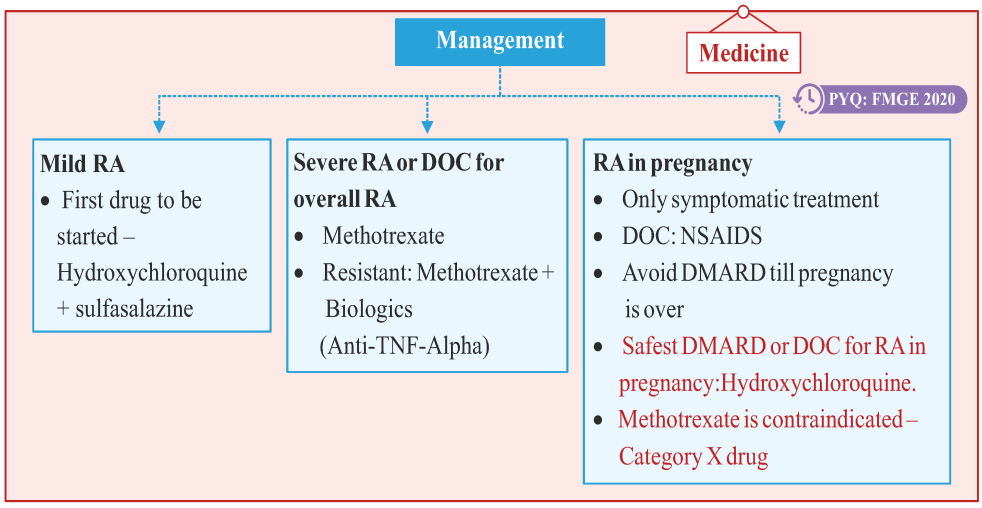
Conventional DMARDS:



Target	Drugs PYQ: FMGE 2022

Anti-TNF-Alpha	• Infliximab - IV route
	• S/C route
	  ○ Certolizumab
	  ○ Adalimumab
	  ○ Golimumab
	  ○ Etanercept

Anti-IL-6	Tocilizumab, Sarilumab
Anti-CD-20	Rituximab
Anti-IL-1	Anakinra
Recombinant CTLA4	Abatacept
JAK inhibitors • **Janus kinase (-nib)**	• Tofacitinib: Inhibit JAK 1 and 3. • Baricitinib: Inhibit JAK 1 and 2. • Upadacitinib: Inhibits JAK 1 only.



Conventional drugs

Methotrexate - Anchor drug, antifolate drug 00:16:55

MOA: Kill lymphocytes

- Antifolate action by inhibiting DHGR
  - DHFR (dihydro folate reductase) converts the folic acid into tetrahydrofolate, which activates the cell division of lymphocytes
- Inhibit thymidylate synthase enzyme
- Inhibit adenosine deaminase
  - Adenosine comes inside the blood vessel as it is not degraded, and kills the lymphocytes
  - Drug causing adenosine efflux – Methotrexate

Dose

- RA: 10-25 mg/week – At low doses, acts as an immunosuppressive drug
- Anticancer: 100 mg/day

Uses

- Most effective drug for RA
- Also used in severe RA
- Action starts >1 month

Methotrexate resistant cases

- Anti-TNF-Alpha or CD-20 inhibitors or any other biologics as per the patient's condition is used along with methotrexate

Side effects

- Megaloblastic anemia
- Hepatotoxicity
- ILD/Pulmonary fibrosis

Monitoring

- CBC
- LFT
- Chest X-ray

Antidote for toxicity

- Folinic acid
- Also known as Leucovorin or Citrovorum factor

Contraindication

- Pregnancy – Causes neural tube defect (Spina bifida)
- Lactation

Leflunomide

00:25:25

Leflunomide

- It is a pro-drug; the active form is teriflunomide

Uses

- Leflunomide – RA
- Teriflunomide – MS

MOA

- Inhibits - DHOLD (Dihydro orotate dehydrogenase) → reduces pyrimidine synthesis →Lymphocytes will not divide
- Thymidylate synthase

Side effects

- Megaloblastic anemia
- Hepatotoxicity

Dose

- 100 mg oral loading dose

Important Information

- Drugs for RA which are hepatotoxic: **MAL**
  - **M**ethotrexate
  - **A**zathioprine
  - **L**eflunomide
- If these drugs are combined- They increase the risk of liver damage.

Chloroquine

00:29:40

MOA

- Used in malaria and also reduces inflammation and body immunity – used in autoimmune disease and hypersensitivity disease like RA
- Inhibits the IL1, IL6 TNF-Alpha production in lymphocytes
- Highest volume of distribution (>15000 L)
- If given on a long-term basis, the drug may be deposited in all organs

Side effects

- Brain – Hallucinations and seizures
- Heart – QT prolongation →↑Risk of arrhythmia
- Ear – Tinnitus and deafness

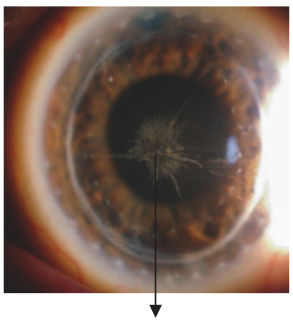
Hydroxychloroquine

- Longer-acting drug with fewer side effects than chloroquine
- More water soluble and doesn't enter the cells, remains in the blood to show its action

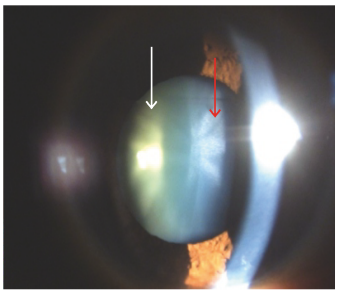
Ophthalmology

Visual side effects of chloroquine

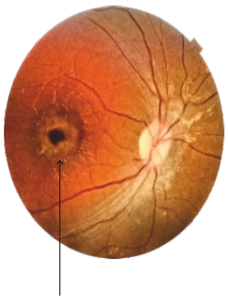
- Deposits in cornea, lens, and retina
- Cornea
  - Deposits like a bunch of flowers – Vortex keratopathy or cornea verticillata
  - Also, caused by amiodarone
- Lens
  - Posterior subcapsular cataract
  - Also caused by glucocorticoids
- Retina
  - Deposits like concentric rings – Bull's eye retinopathy causes permanent blindness



Vortex keratopathy



Posterior subcapsular cataract



Bull's eye retinopathy

Important Information

- Hydroxychloroquine has fewer visual side effects than chloroquine.

Sulfasalazine

00:35:35

Sulfasalazine

- Prodrug
- Comes under sulfonamides

Two active forms

- Linked by an 'AZO' bond
- Sulfapyridine
- 5-amino salicylic acid
- Colonic bacteria breaks the azo bond and the sulfapyridine absorbed into the blood
  - Kills lymphocytes

5-amino salicylic acid

- Used in ulcerative Colitis
- One drug with two different uses
- Only 5-ASA for t/t UC – SALA
  - Mesalazine, also known as mesalamine
  - Olsalazine
  - Balsalazide

Side effects

- Sulfa allergy
- Contraindicated in G6PD deficiency, as it may damage the RBC and cause hemolysis
- Reduces sperm count

Azathioprine and other miscellaneous drugs

- Other miscellaneous drugs - **Reserved drugs:** Used in RA + Other systemic Organ involvement (Eg., ILD)
  - Cyclosporine
  - Cyclophosphamide
  - Chlorambucil

00:40:50

Penicillamine

- Additional use – Copper chelator used in Wilson's disease

Gold – Au

- **Drugs**
  - Aurofin
  - Aurothiomalate

Side effects

- Old drugs and rarely used due to high toxicity
- Most common: diarrhoea
- Dermatitis
- DLE
- Damage kidney – Highly nephrotoxicity drugs

Biologics

00:42:55

Anti-TNF-Alpha- Infliximab - IV

Uses

- Used in methotrexate – resistant cases, like
  - **R**A
  - **U**lcerative colitis/Crohn's disease (IBD)
  - **P**soriatic arthritis
  - **A**nkylosing spondylitis

Structure

- Upper Fab (TNF-Alpha receptor derived from mouse) + Lower FC (Human IgG1) fragments
- Eternecept – The Fc portion is absent and only the receptor part is present

Side effects

- Suppress TNF – Alpha, which is necessary to suppress diseases like tuberculosis → Reactivation of latent TB (Perform Montoux test or PPD test; if positive, avoid the drug)
- Increased risk of lymphoma
- Increased risk of HBV/HCV

Contraindications

- MS and vitiligo (Humoral autoimmune diseases), as the disease may aggravated

Anti-IL 6

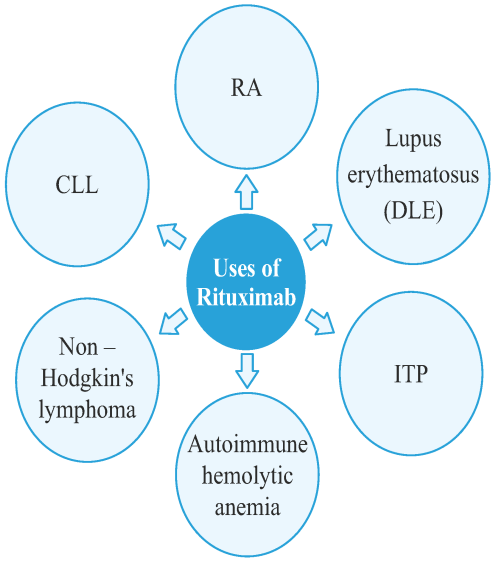
- Tocilizumab and sarilumab
  - Dosage form - Injection
- Used in RA, and cytokine storms (COVID-19)

Anti-IL-1

- Anakinra - Used in RA

Anti-CD20

- B-lymphocytes CD20 receptors are blocked, and the drug kills lymphocytes.



Recombinant form of CTLA4 receptor

- Abatacept
  - **Treatment:** RA
  - APC activates the CD28 receptor of lymphocytes and stimulates inflammation.
  - CTLA4 receptor, a negative stimulant, inhibits the CD28 receptor.
- Belatacept - Reduce immunity in organ transplantation.

JANUS Kinase inhibitors (JAK inhibitors)

- Drug name ends with - **Nib**
  - Tofacitinib- Inhibit JAK 1 and 3 (Also used in IBD)
  - Baricitinib- Inhibit JAK 1 and 2
  - Upadacitinib- Inhibits JAK 1 only
- **Uses**
  - All ILs, and TNF-Alpha, act upon the JAK-STAT receptors to produce inflammation.
  - **JAK enzyme inhibition** → Reduces inflammation.
- Only oral biological DMARD is JAK inhibitor

26 RENAL DIURETICS

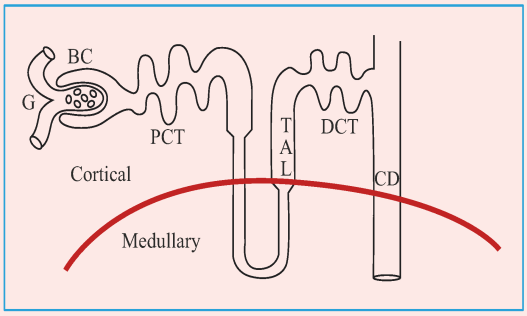
Diuretics
Increase urine volume – Measured as urinary flow rate

Increase Na+ excretion in urine
- Drugs – Natriuretics

Increased water excretion through urine
- Drugs – Aquaretics

Physiology of Nephron

Physiology



PCT

Sodium enters nephron via afferent arteriole

↓

Reabsorbed back into the blood at PCT through carbonic anhydrase enzyme

↓

This enzyme also reabsorbs the bicarbonate ion

↓

60% of sodium is reabsorbed at the level of PCT

Limb of Henle

Desceding limb, Loop of Henle and Ascending limb of Henle

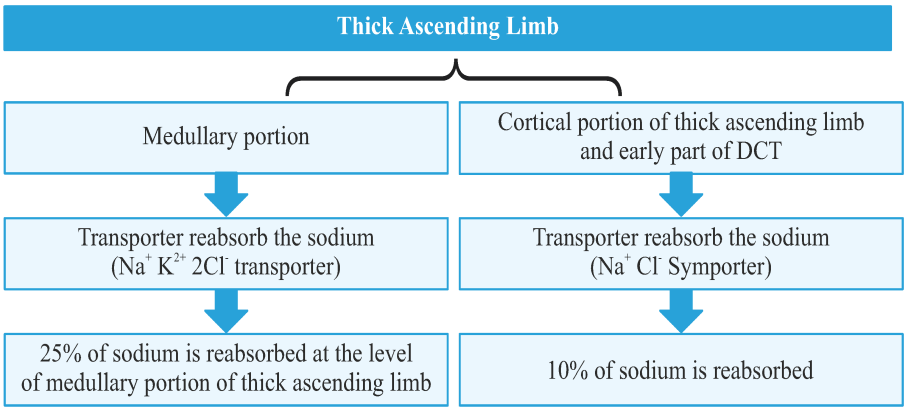
↓

Water is reabsorbed

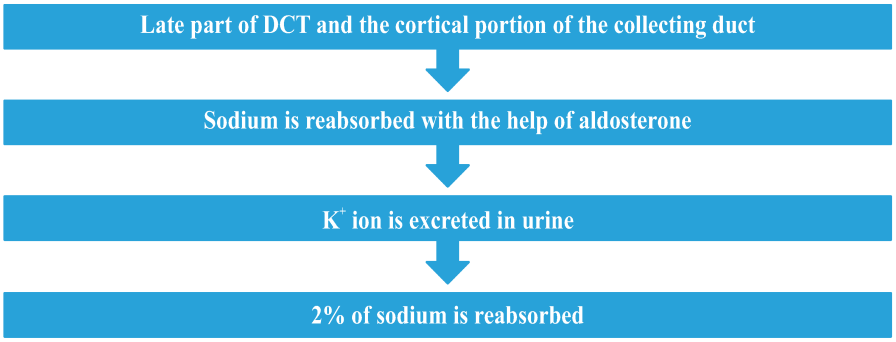
↓

Impermeable to sodium

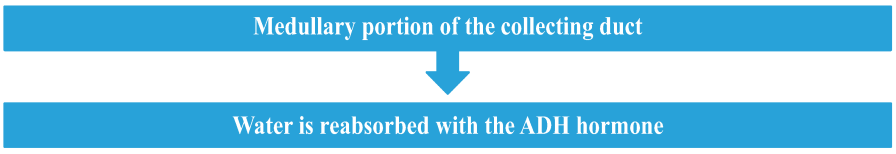
Thick Ascending Limb and Early Part of DCT



Late Part of DCT and Cortical Portion of Collecting Duct



Medullary Portion of Collecting Duct



Classes of Diuretics

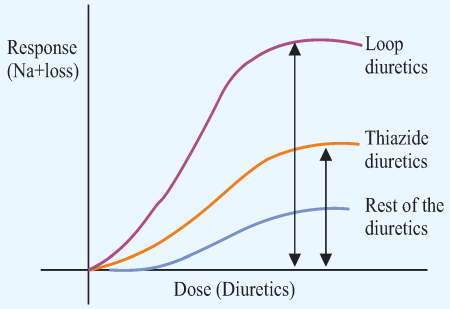
00:08:50

PYQ: FMGE 2020, 2021, 2022, 2023

Types	Mechanism	Act on
Carbonic anhydrase inhibitors • Acetazolamide	PCT of nephron and inhibit carbonic anhydrase enzyme	Na^+/HCO_3^- excretion in urine
Osmotic diuretics • Mannitol	Acts on descending limb of Henle/loop of Henle	Inhibit reabsorption of water
Loop diuretics • Furosemide	Na^+ K^+ $2Cl^-$ transporter inhibitors	Acts on the medullary portion of the thick ascending limb
Thiazide diuretics • Chlorothiazide	Inhibition of Na^+Cl^- symporter	Cortical portion of thick ascending limb + early part of DCT
K^+ sparing diuretics • Spironolactone	Inhibit the action of aldosterone	Late part of DCT and the cortical portion of the collecting duct

- Most effective diuretic causing max sodium loss- Loop diuretics
- Carbonic anhydrase inhibitors- Weak diuretics

00:13:47



- Most effective diuretic: Loop diuretics (aka High ceiling diuretic) followed by thiazide diuretics (aka Medium ceiling diuretic)
- Rest of the diuretics- Weakest
  - Other Name- Low ceiling diuretics
  - Examples- Osmotic diuretics, carbonic anhydrase inhibitors, K^+ sparing diuretics
  - Least effective- K^+ sparing diuretics (Only 2% sodium is reabsorbed at the collecting duct)

Maximum sodium loss	• Loop diuretics > Thiazides > Osmotic diuretics > Carbonic anhydrase inhibitors> K^+ sparing diuretics
Maximum potassium loss	• Carbonic anhydrase inhibitors > Thiazides > Loop diuretics > Osmotic diuretics • Na^+ absorption is inhibited in the proximal part of the nephron

K^+ Sparing Diuretics

- Preserve potassium
- Used as an add-on drug with other diuretics
  - Prevents hypokalemia
  - Shows synergism
- A combination of diuretics shows synergism
  - Additive Na^+ loss
  - Reduce the risk of hypokalemia

Some Other Miscellaneous Diuretics

00:20:55

Theophylline and caffeine

- Drug used in asthma – Theophylline PYQ: NEET PG 2020
- Drug used in migraine – Caffeine
- Causes blockage of adenosine A1 receptor on nephron

Natriuretic peptides

- Includes
  - Atrial Natriuretic peptides
  - Brain Natriuretic peptides
    → Nesiritide – Used in heart failure
- Act on enzyme linked receptors on nephron
  - Attach to guanylyl cyclase and increase CGMP leading to sodium loss in urine

SGLT-2 Inhibitors

- Recommended in diabetes mellitus
- Inhibit sodium glucose transporter in nephron
  - Na^+ loss + Glycosuria
- Drugs ends with the word - flozin
  - Canagliflozin
  - Empagliflozin
  - Dapagliflozin

Mechanism of Action

Act on the PCT of nephron → Inhibits carbonic anhydrase enzyme → Na^+/HCO_3^- excretion in urine

Drugs

- Acetazolamide
- Methazolamide
- Dichlorphenamide
- Derivatives of antibiotics – Sulfonamide (causes severe allergic reactions)
  - Acetazolamide like drugs are contraindicated in sulfa allergy
- These drugs are non competitive and irreversible inhibitor
  Except acetazolamide – Non competitive and reversible inhibitor of carbonic anhydrase enzyme
- Topical eye drops – Recommmended in glaucoma
  - Brinzolamide
  - Dorzolamide

Uses of Acetazolamide Like Drugs

- Mnemonic- GAME Plan

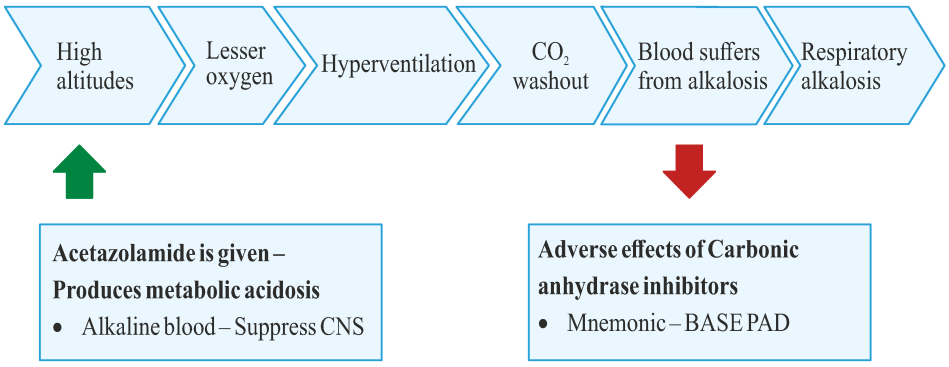
	Action	Uses
G- Glaucoma	• Most abundant enzyme- Carbonic anhydrase ○ MOA- Decrease aqueous secretion from ciliary cells	**Eye drops of Brinzolamide, Dorzolamide** • Given in primary open-angle glaucoma **IV drugs- Acetazolamide** • Emergency- Acute congestive glaucoma
A- Alkalinization of urine	• Bicarbonate excretion **Side effects** • Increases the risk of alkaline renal stones • Increase the risk of calcium phosphate stones **Treatment** • Thiazide diuretics • Inhibits calcium excretion	• Acidic drug poisoning • Acidic stones in the kidney ○ Uric acid stones ○ Cystine stones-Homocystinuria
M- Metabolic acidosis in blood	• Increased H^+ ions in blood	• Acetazolamide- DOC for mountain sickness
E- Epilepsy	• Suppresses the activity of neurons	• Acetazolamide was earlier used for epilepsy
P- Periodic muscle paralysis	• Imbalance of potassium ion in blood • Occurs due to ○ Hyperkalemia ○ Hypokalemia	• Acetazolamide is used in periodic muscle paralysis

Mountain Sickness (aka Altitude sickness)

00:33:55

- DOC- Acetazolamide
- ROA- Oral

PYQ: FMGE 2021



Suppress CNS – Slowly Stops the Breathing Leading to Respiratory

B- Bone marrow suppression	• Due to sulfa allergy
A- Increase Ammonia level in blood	• Ammonia retention Urine is produced in nephron → Ammonia is converted into ammonium ion by H^+ → Ammonia is excreted in acidic urine → Ammonium ion is excreted in urine Reabsorption of ammonia in to the blood → Ammonia is not converted into ammonium → No H^+ ion in urine → When Acetazolamide like drugs are given Liver converts ammonia into urea → If liver disease is present → Ammonia is not converted to urea → Damage the brain neurons • Contraindication of acetazolamide-like drugs- Liver disease ○ Causes hyperammonemia encephalopathy
S- Stones in the kidney	• Increase in calcium phosphate stones • Treatment- Thiazides

E- Electrolyte imbalance in blood	• Causes K^+, HCO^3 loss in urine ○ The blood level of H^+ is increased ○ Hyperchloremic Hypokalemia- Metabolic acidosis ○ The kidney retains the chloride ion • Causes hyperchloremic hypokalemic metabolic acidosis
P- Paresthesia	• Tingling sensation in hands and feet
A- Allergy	• Due to sulfa
D- Diarrhea	• Most common
S- Stones in the kidney	• Increase in calcium phosphate stones • Treatment- Thiazides

Loop Diuretics

00:42:08

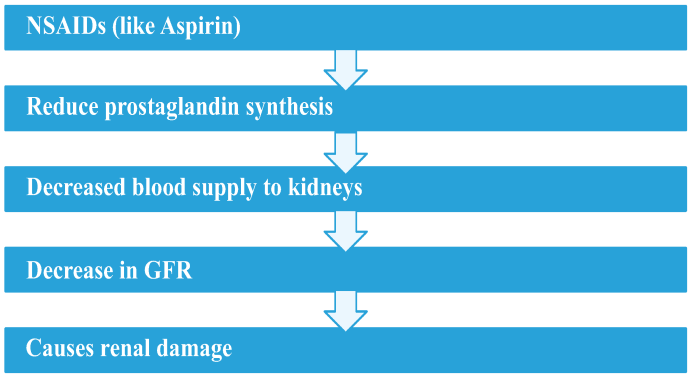
Mechanism of Action

MOA-1	MOA-2	MOA-3
• Act on the medullary portion of the thick ascending limb ○ $Na^+K^+2Cl^-$ transporter inhibitors	• Inhibits water reabsorption- Reduce medullary hyperosmolarity Thick ascending limb ↓ Reabsorption of sodium ↓ Increase the osmolarity of medulla ↓ Reabsorption of water into the medulla	• Increase the synthesis of prostaglandins in nephron Prostaglandin ↓ Dilated the blood vessels in nephrons of kidneys ↓ Increase in blood supply ↓ Increase in GFR ↓ Increased urine production

- Diuretic of choice in renal disease- Loop diuretics

Drug Interactions of Loop Diuretics

- Aspirin + Loop diuretics- The action of loop diuretics is reduced



Drugs Under Loop Diuretics 00:48:03

Mercury Containing → MERSALYL	Not used: Highly ototoxic (Prominent deafness)
Phenoxy-acetic Acid → Ethacrynic acid	Yes: Less Ototoxic
Sulfa Containing → Furosemide (Frusemide) Bumetanide: Most potent Toresamide: longest acting	

- ROA- All routes
  - Oral
  - Emergency- IV, IM

Uses of Loop Diuretics

Acute pulmonary edema – DOC

- Other Name – Acute left ventricular failure
- Treatment – Reduce preload
- Drugs – Venodilators
- Loop diuretics – Increase prostaglandin production
- Morphine – Increase the production of histamine
- Nitroglycerin – Increase nitric oxide production

Severe hypertension

PYQ: FMGE 2023

- Diuretic of choice – Thiazide
- Not effective when BP is > 160/100 mmHg
- Only in case of Severe hypertension Loop diuretics is used

Hyperkalemia, Hypercalcemia, Hypomagnesemia in blood – DOC

- Help in excreting K^+, Ca^{2+}, Mg^+ in urine

Edema - DOC

- Acute volume overload in body

Edema

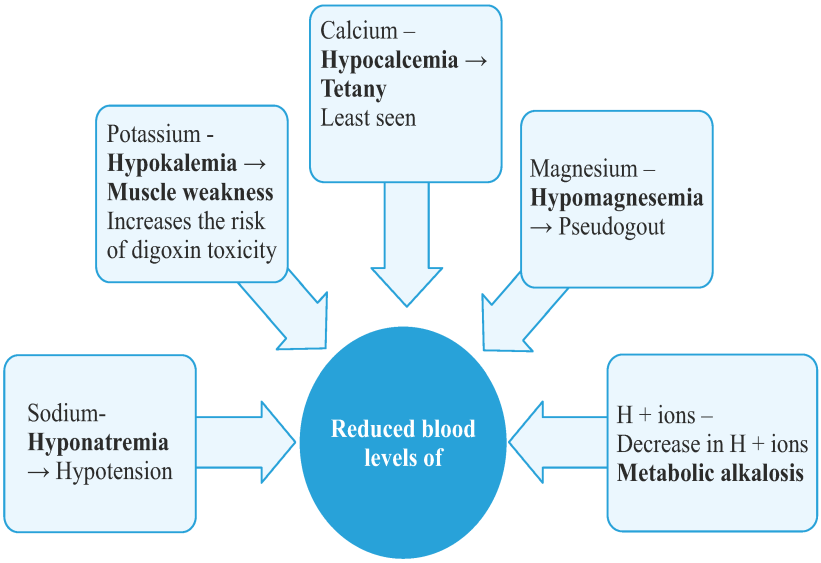
- Increase in fluid in the body
  - Due to increased hydrostatic pressure
  - Decrease in plasma oncotic pressure

Causes of Edema

Heart failure	• LVF: Pulmonary edema • RVF: Pedal edema • Severe RVF with LVF: Anasarca	Diuretic of choice - Loop Diuretics
Renal failure	• CKD/Nephrotic syndrome – Periorbital edema	
Liver failure	• Portal hypertension • Classic edema – Ascites	Diuretic of choice - Spironolactone
Cerebral edema	• Increase in CSF pressure or ICP	Diuretic of choice - Mannitol

- Diuretic of choice in case of Refractory edema- Loop diuretics
- Mannitol is an absolute contraindication in heart and renal failure

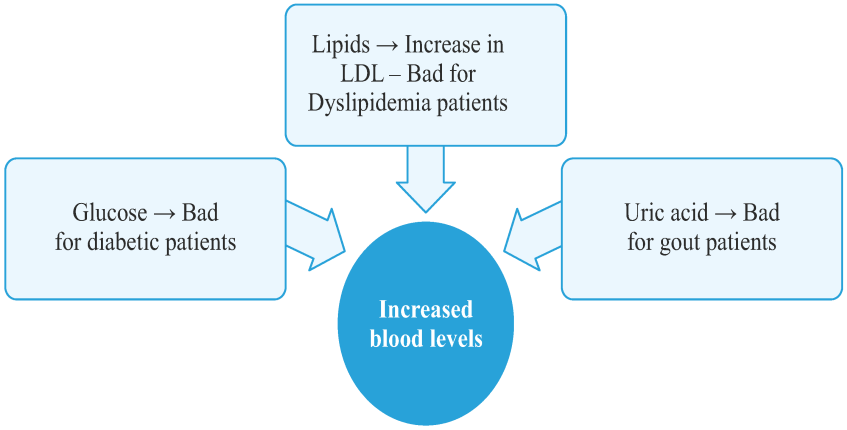
Adverse Effects of Loop Diuretics



- The same effects are also seen with Thiazides
  - Except- Calcium

Important Information

- Loop diuretics reduce calcium whereas thiazide diuretics increase the calcium levels



- The same effects are also seen with Thiazides

Loop Vs Thiazide Diuretics

		Urine Ca^{2+}	Blood Ca^{2+}	Use
Loop	Lose calcium in urine	High	Low	Treat hypercalcemia in the blood
Thiazides	Preserve calcium in the blood	Hypocalcemia	Hypercalcemia	Treat hypercalciuria S/E: Calcium-containing renal stones (Treat)

Thiazides

MOA

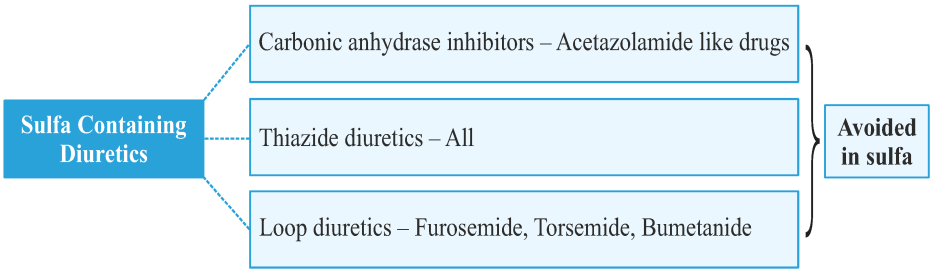
- Acts on the cortical portion of the thick ascending limb and early part of DCT
  - Other Name- Distal tubule
  - Inhibit Na^+Cl^- symporter

Thiazide	Thiazide like

• Chlorothiazide
• Hydrochlorothiazide
• Bendroflumethiazide
PYQ: NEET PG 2020
	• Chlorthalidone – Longest acting PYQ: INICET 2021
	• Metolazone – Safe in renal failure
	  ○ Add on drugs to loop diuretics
	• Indapamide – Most potent
	  ○ Safe in renal failure (GFR < 30 ml/min)

Uses of Thiazide Diuretics

DOC for Hypertension	Produce persistent Na+ loss → Vasodilation → Reduces diastolic blood pressure • Not effective in severe hypertensive emergency (>160/100mmHg) • DOC- Loop diuretics
DOC for the treatment of hypercalciuria	• Increases Na^+Ca^{2+} exchanger • Increase the effect of parathyroid hormone • Eg: Dent disease ○ DOC- Thiazide
DOC for Diabetes insipidus PYQ: FMGE 2020	• Nephrogenic diabetes insipidus • Have antidiuretic property Diabetes insipidus → Defect in ADH hormone → Polyuria and urine is hypoosmolar in nature Tubuloglomerular feedback → Reduce positive free water clearance → Increase in urine osmolarity Reduce GFR → Decrease in urine volume → Produce antidiuretic effect Thiazides – Prevent sodium → Sodium loss in urine

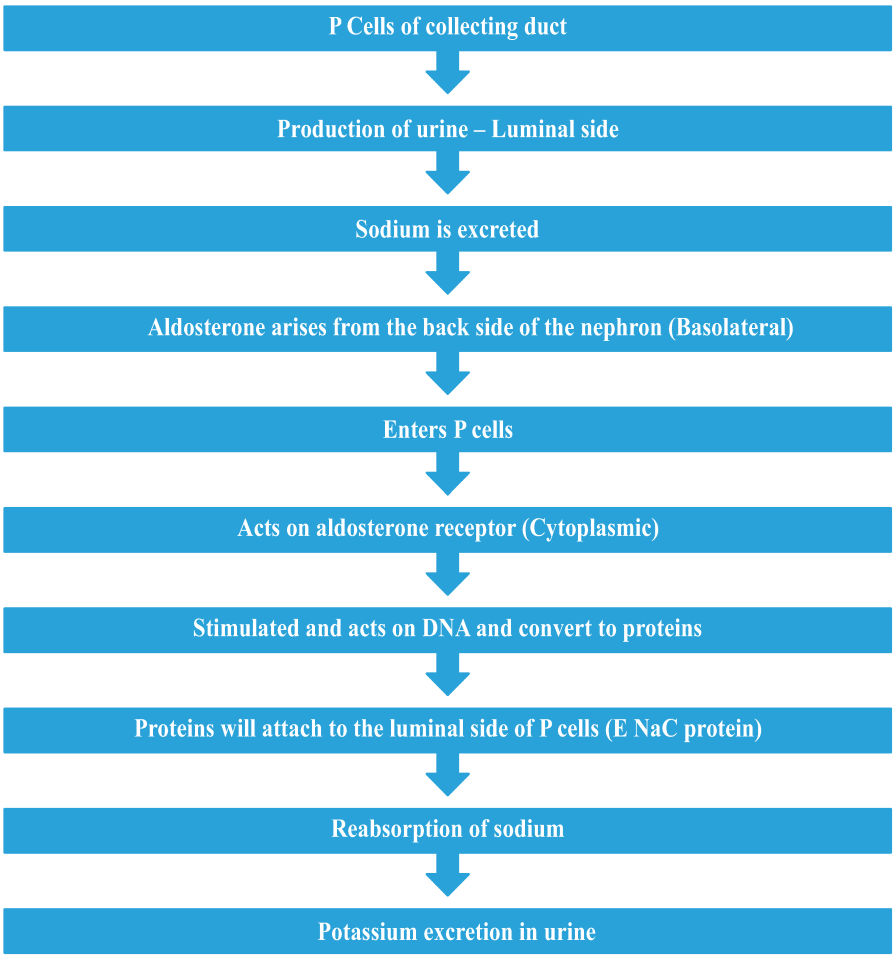


K^+ Sparing Diuretics

01:19:55

Mechanism of Action

- Inhibits the action of aldosterone at the level of the collecting duct and late part of DCT



Drugs of K+ Sparing Diuretics		
Aldosterone receptor antagonists	• Drugs ○ Spironolactone ○ Eplerenone	Acts from the basolateral side of the nephron
ENaC Inhibitors	• Drugs ○ Amiloride ○ Triamterene	Acts from the luminal side of the nephron

- All diuretics act from the luminal side of the nephron
  - Except spironolactone, Eplerenone
- K^+ sparing diuretics are combined with other diuretics as they result in hypokalemia
  - Loop diuretics
  - Thiazides
  - Carbonic anhydrase inhibitors

Aldosterone Antagonists 01:27:08

Spironolactone

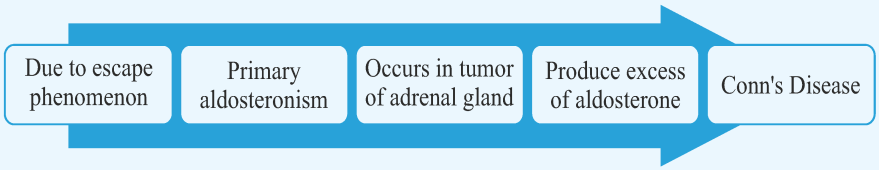
- Active drug
- Active form in the body- Canrenone
- ROA- IV, oral
- MOA
  - Blocks aldosterone receptor
  - Also blocks testosterone receptors in males and females
    → Males- Gynecomastia, impotency
    → Females- Treats hirsutism (PCOD)
- Eplerenone- Doesn't produce gynecomastia or impotency-like signs

Uses of Spironolactone and Eplerenone

ENaC Inhibitors 01:33:56

DOC for Primary Hyperaldosteronism

- Patients don't suffer from hypertension and edema



DOC for Secondary Hyperaldosteronism

- Patients suffer from hypertension and edema.
- There is an increase in RAAS activity → excess production of aldosterone. It is seen in
  - Chronic liver disease (L/t ascites)
  - Chronic heart failure

New drugs – Finerenone

- Approved to protect kidney in case of diabetic nephropathy
  - DOC-ACE inhibitors
- It is given as add on drugs to ACE inhibitors

Amiloride

- Longer acting and less side effects
- Uses:
  - DOC for liddle syndrome
    → Genetic disease which causes ENaC channels to be more active

DNA in the collecting duct is mutated → DNA not under the control of aldosterone hormone → No role of spironolactone → Blockage of ENaC Channels

- DOC for lithium toxicity
  - Li^+ is reabsorbed back from ENaC channels

Triamterene

- **Side effects**
  - F-Folic acid deficiency
  - I – Interstitial nephritis
  - R – Renal stones

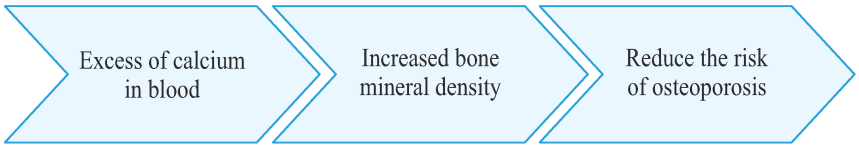
Lithium

- Li+ is reabsorbed from urine back into blood through ENaC — PYQ: FMGE 2021
- Lithium toxicity- DOC: Amiloride, mannitol — PYQ: NEET PG 2020
- Loop and thiazides- Blocks Na+ reabsorption from proximal part of nephron
  - Increase the amount of ENaC in the kidney
  - Increase the risk of lithium toxicity

Summary of Diuretics

Diuretics	Blood Na^+	K^+	H^+	Ca^+	Mg^+	Produce
Carbonic anhydrase inhibitors	↓	↓	↑	↓	↓	Hypokalemic metabolic acidosis
Loop diuretics	↓	↓	↓	↓	↓	Hypokalemic metabolic alkalosis
Thiazides	↓	↓	↓	↑	↓	
K^+ sparing	↓	↑	↑	↑	↑	Hyperkalemic metabolic acidosis
Osmotic	↓	↓	↓	↓	↓	Hypokalemic metabolic alkalosis

- Preserve calcium- Thiazides > K+ sparing diuretics
  - DOC- Hypocalcemia (Thiazides)



- Preserve magnesium- Potassium-sparing diuretics
  - DOC- Amiloride (for Hypomagnesemia)

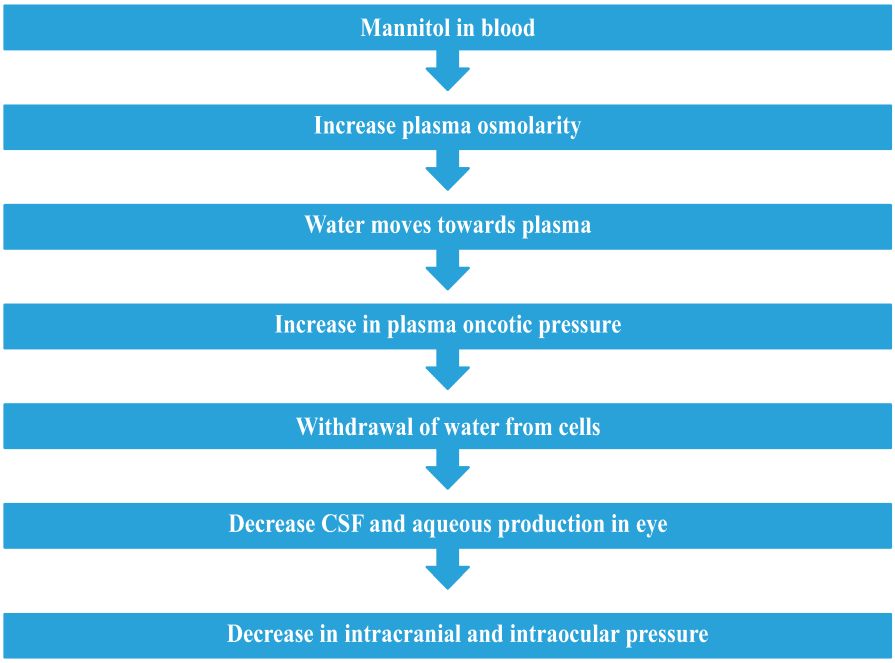
PYQ: NEET PG 2020

Osmotic Diuretics

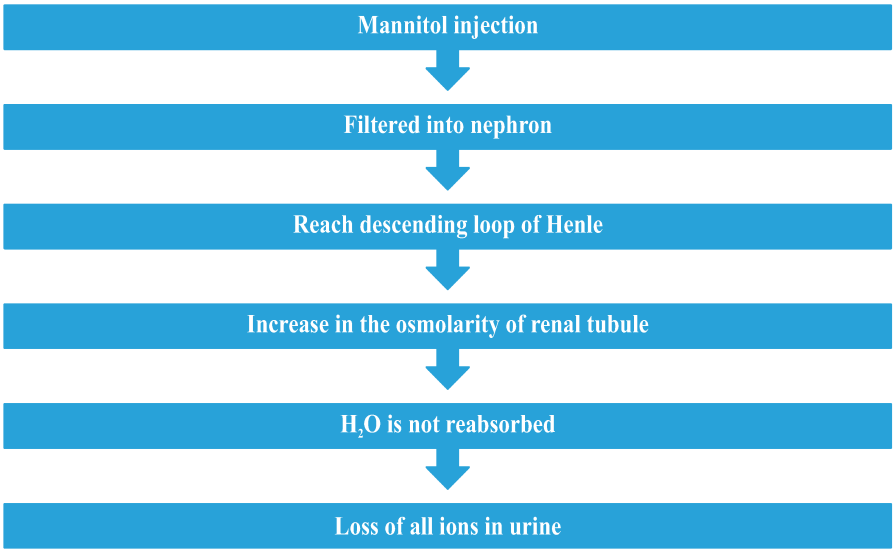
01:44:50

- Drugs- MIGU
  - **Mannitol** (IV)
    - → Osmolarity- 20%
    - → Uses:
      - DOC in Cerebral edema
      - Emergency- Acute glaucoma
      - Dialysis disequilibrium
  - **Isosorbide** (Oral, rectal)
  - **Glycerol** (Oral, rectal)
  - **Urea** (IV)

MOA



- Side effects- Increased plasma volume
- Contraindication- Heart failure
  - Increase in preload



- High amount of lithium and platinum- Excreted when mannitol is administered
- Mannitol
  - DOC- Lithium toxicity, cisplatin toxicity

27 RENAL ADH

Introduction

ADH

- Also known as vasopressin
- **Synthesis: Hypothalamic neuron**
  - Supra-optic nucleus
  - Paraventricular nucleus
- **Secretion:** Posterior pituitary

Receptors (G Protein-Coupled)

Physiology 00:00:45

V_1 (V_1A)	V_2	V_3 (V_1B)

• Gq type
• Second messenger: Increase IP3/DAG
• Effect: Vasoconstriction
  ○ Increase BP
  ○ Can be used in the treatment of shock
	• Gs type
	• Second messenger: Increase cAMP
	• Present in
	  ○ Endothelial cells of blood vessels - Increases vWF and Factor 8
	  ○ Nephron - Acts on collecting duct increasing aquaporin II production reabsorbs water from urine)
		• Gq type
		• Second messenger: Increase IP3/DAG
		• Present in brain neurons (a neuropeptide)
		• Increases ACTH and endorphins (stress hormone)

Vasopressin Agonists

00:04:20

- End with the word "PRESSIN"

Natural

- **Arginine Vasopresssin**
  - Human Vasopressin
  - Short-acting
- **Lysine Vasopressin (Lypressin)**
  - Obtained from swine (pig)
  - Long-acting

- Act on all 3 receptors (V1, V2 and V3 agonist)
- Both are used in the treatment of shock resistant to epinephrine and norepinephrine

Examples

- Cardiac arrest
- Septic shock
- Cardiogenic shock

- Route of administration (ROA) - These drugs are given in injections only, since they are not absorbed orally

Synthetic

Medicine

	Properties	Uses
Terlipressin	• V_1 agonist • Given by Injections only	• DOC to control bleeding esophageal varices • DOC for hepatorenal syndrome • Also given in resistant shock
Felypressin	• V_1 agonist • Given by Injections only	• Given as add on to local anesthetic • Epinephrine is also used • Epinephrine > Felypressin

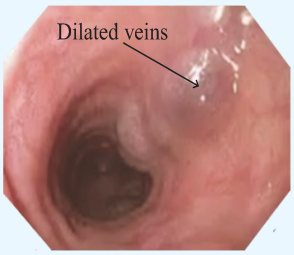
Desmopressin	• Also called DDAVP
	• V_2 agonist
	• Only vasopressin which is given orally and nasally
	• Longest acting drug
	• Most potent drug- Least dose needed (not easily degraded in the body)
	Side effect:
	• Dilutional hyponatremia
	  ○ Nausea and vomiting
	  ○ Seizures
		• Used in the treatment of Hemophilia A (Factor 8 deficiency)
		• DOC for nocturnal enuresis (bed wetting)
		• DOC in neurogenic diabetes Insipidus

Esophageal Varices

Surgery

00:13:23

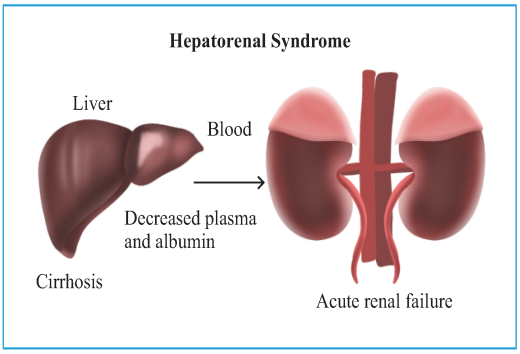
Esophageal Varices



- **Most common cause:**
  - Liver diseases → portal hypertension → esophageal varices.
  - Complication : Rupture of portal vein → hematemesis.
- **Treatment of acute bleeding**
  - DOC is Terlipressin > IV octreotide
  - **Maintenance:** Propranolol is used

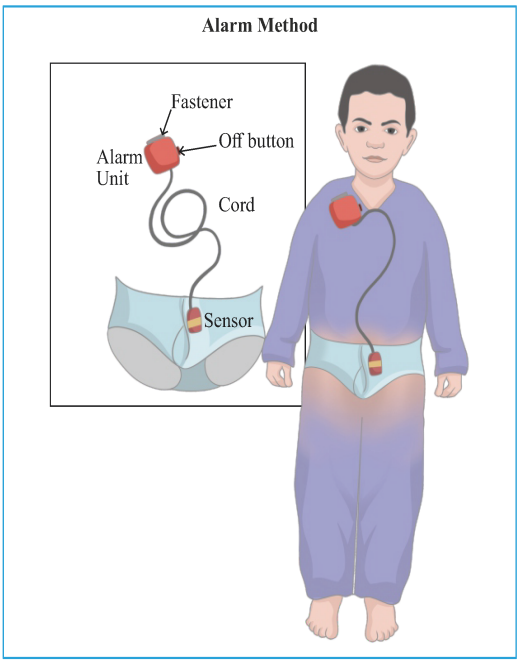
Hepatorenal Syndrome

00:15:28



- **Treatment**
  - Blood or plasma
  - Albumin
  - The addition of Terlipressin produces vasoconstriction and increases blood supply to the kidneys.

Nocturnal Enuresis — Pediatrics — 00:17:04



Bedwetting by a child > 6 years requires treatment

1st treatment: Lifestyle modification
- Alarm method
  - An alarm is placed near the urinary tract of the child
  - When urine is passed it rings and wakes up the child
- Decrease water intake before sleep
- Pelvic muscle exercise

Drugs are used if lifestyle changes fail

Desmopressin – DOC
- Synthetic ADH
- Decreases urine volume
- ROA: Oral, nasal spray

Oxybutynin
- Anticholinergic
- Relaxes detrusor muscle of the bladder
- ROA: Oral

Imipramine
- Tricyclic antidepressant
- Has anticholinergic property

Vasopressin Antagonists

00:20:54

- End with "VAPTAN"

Vasopressin Antagonists

Conivaptan
- V_1 and V_2 antagonists

V_2 antagonists
- Tolvaptan
- Lixivaptan
- Mozavaptan

Demeclocycline
- Tetracycline group
- V_2 antagonist

Used in the treatment of SIADH (syndrome of inappropriate ADH) secretion
Characterized by dilutional hyponatremia

Causes
- CNS (most common): Trauma, tumors
- Small cell lung cancer
- Liver disease
- Heart disease

Important Information

New Drug- Balovaptan
- V_1 antagonist
- Approved for autism

SIADH (Syndrome of Inappropriate ADH Secretion)

00:23:55

- Excess water reabsorption from kidney back into the blood leading to Hyponatremia

Acute Hyponatremia	Chronic Hyponatremia
• **Pathology** – A sudden decrease in sodium • **DOC:** Hypertonic saline (Increase Na^+) • After the hypertonic saline, loop diuretics should be given (reduces Na^+ and water level)	• **Pathology** – Slow decrease in sodium • Fluid or water restriction from outside • **Rx:** Tolvaptan (DOC), Demeclocycline

Diabetes Insipidus

00:27:00

Pathophysiology:

- Defect in ADH hormone

- **Clinical features**
  - Polyuria
  - Dilute urine

- **2 types**

Neurogenic Diabetes Insipidus	Nephrogenic Diabetes Insipidus
• Lack of ADH secretion by hypothalamus • Central diabetes insipidus • **DOC:** Desmopressin • Other drugs (Increases ADH secretion from brain) ○ Chlorpropamide (also used in diabetes mellitus) ○ Carbamazepine	• ADH secretion is present but ADH receptors are non responsive • Desmopressin is not effective • **DOC:** Thiazide diuretics • Sometime Indomethacin (NSAID) is added • Lithium causes Lithium induced nephrogenic diabetes insipidus ○ **DOC:** Amiloride

Important Information

- Thiazides and Indomethacin can be used in both types of diabetes insipidus

Free Water Clearance

00:32:38

In urine

- Sodium and water is excreted in similar ratio
- If this is equal to plasma it is called normal free water clearance

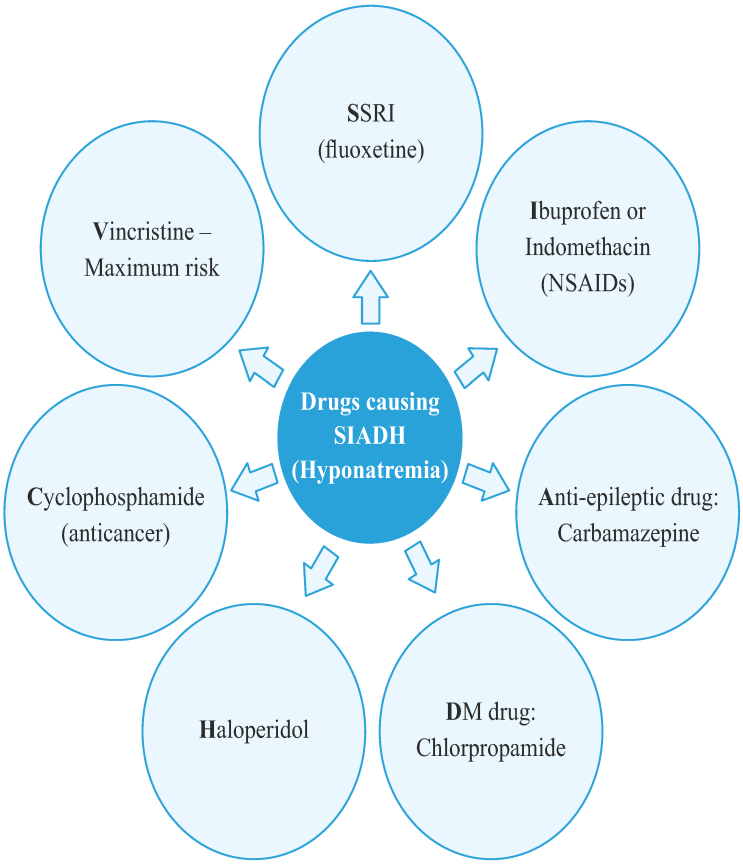
In diabetes insipidus

- Excretion of water is more than sodium
- Excess positive free water clearance
- Thiazides are used
  - Acts at cortical region ($Na^+ >> H_20$ loss in urine)
  - Reduce positive free water clearance

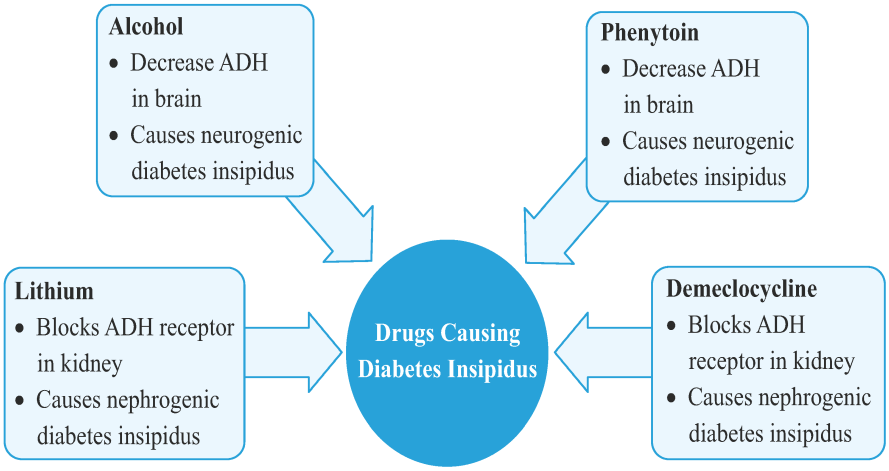
SIADH

- Excretion of sodium is more than water
- Excess negative free water clearance
- Loop diuretics are sued
  - Acts at medullary region ($Na^+ = H_20$ loss in urine)
  - Reduce both positive and negative free water clearance

- **Mnemonic- SIADH Cannot Void**



- **Mnemonic- LAP Dog**

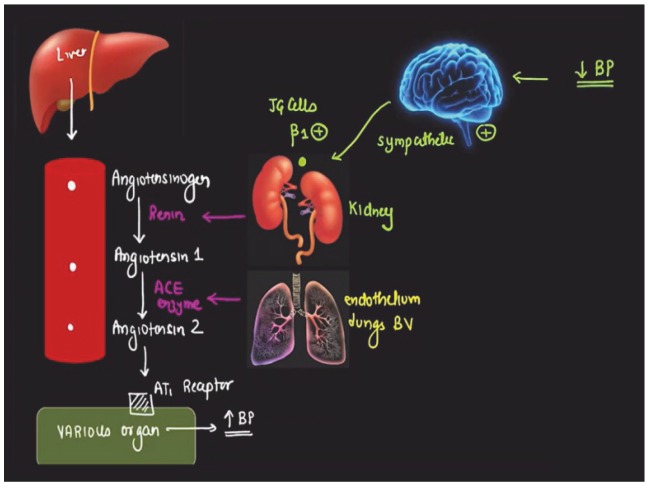


28 RAAS INHIBITORS

- Renin angiotensin aldosterone system
- Function: Increases BP
  - Antihypertensives

Functioning of RAAS System

00:00:50



Angiotensinogen (inactive form) synthesised by the liver enters the blood vessel

↓

Produces vasoconstriction

↓

↓ BP

↓

Stimulates neurons in brain

↓

Sympathetic discharge

↓

Stimulates β1 receptors in JG cells of kidney

↓

Causes renin release

↓

Converts angiotensinogen to angiotensin 1 (active form)

↓

Angiotensin 1 is converted to angiotensin 2 by ACE enzyme present in endothelial cells of lung

↓

Angiotensin 2 acts on AT1 receptors of various organs

↓

↑BP

- Adrenal glands: release aldosterone
  - Sodium reabsorption
    → Increase in sodium in blood leads to increased BP
  - Potassium loss
- Arteries & veins: Vasoconstriction
- Heart: Cardiac stimulation
  - Cardiac hypertrophy (CHF)

Drugs

PYQ: FMGE 2020, 2023

- Direct Renin Inhibitor (Kiren)
  - Aliskiren
- ACE inhibitor (Pril)
  - Lisinopril
  - Captopril
- AT1 receptor blockers (Sartan)
  - Losartan
  - Telmisartan

Other Drugs

- Clonidine
  - Acts on α 2A receptor
  - Decreases sympathetic discharge from the brain
  - Reduce renin secretion
- β blockers
  - Acts on JG cells of kidney
  - Reduces renin release

RAAS Inhibitors

00:08:31

MOA: RAAS Inhibitors OF ACE/ARB

PYQ: FMGE 2023

- Eg; ACE inhibitors/ ARB

Decreases aldosterone secretion from adrenal gland
↓
Causes sodium loss in urine: Diuretic action
↓
Increase in blood potassium
↓
Causes hyperkalemia as side effect

Important Information

- ACE inhibitors like drugs are avoided with potassium sparing diuretics
  - This is because both produce hyperkalemia
- Potassium sparing diuretics:
  - Spironolactone
  - Eplerenone
  - Amiloride
  - Triamterene

- In blood vessels: Vasodilators
- In heart: ACE inhibitors reduce cardiac hypertrophy
  - Also known as cardiac remodelling
    → Hallmark of CHF
  - DOC in CHF

Aliskiren

00:12:50

- Direct renin inhibitor
- Used as an antihypertensive
- S/E and C/I: Same like ACE inhibitors
  - Exception: Doesn't increase bradykinin levels

ACE Inhibitors

- E.g., Captorpil, Lisinopril 00:14:02
- ACE enzyme: Angiotensin 1 convertase enzyme
  - Non specific
  - Carboxypeptidase
  - Located on the surface of endothelial cells of pulmonary vessels
  - Converts Angiotensin 1 to Angiotensin 2
    → Increases BP
  - Degradation of Bradykinin
- ACE inhibitors reduces the level of angiotensin 2
  - Decreases BP
  - Increases the level of Bradykinin

Effect of Increased Bradykinin Levels

- Advantages:
  - It is a vasodilator - Decreases BP
  - Improve insulin action - Favourable for DM
    → DOC in hypertension + DM
- Disadvantages: Allergic reactions (Mnemonic: DARU)
  - Dry cough
  - Angioedema
  - Rhinitis
  - Urticaria
- Angioedema

Angioedema

- Swelling of face & limbs
- Treated by Antihistamines + corticosteroids
- Sometimes involves larynx: Laryngeal edema
  → SC injections of epinephrine are given - produce bronchodilation

- Dry cough
  - Most common side effect of ACE inhibitor
  - 15-20% people
  - Treatment:
    → Stop ACE inhibitor
    → Start AT1 receptor blockers (Stop Prils and Start Sartans)
    → Aspirin, iron tablets are used- Reduces Risk of Dry Cough

Drugs in ACE Inhibitors

00:21:50

- Mnemonic: CRPF BELT QM
  - Captopril
  - Ramipril
  - Perindopril
  - Fosinopril
  - Benazepril
  - Enalapril
  - Lisinopril
  - Trandaloprol
  - Quinapril
  - Moexipril

Captopril	• Not used • Shortest acting drug: <12 hrs • Given twice a day • Sulfa containing drug ○ Dangerous allergic reactions like → Bone marrow suppression → Taste disturbance → Food reduce absorption – Avoided with food
Enalapril	• Given orally • Active form: Enalaprilat(IV) ○ Used in hypertensive emergency
Fosinopril	• Safe in renal disease ○ No dose reduction is required ○ Also excreted in bile
Trandolapril	• Most potent

- All ACE inhibitors are prodrugs
  - Inactive form(pril) gets converted to active form(prilat)
  - Except: Captopril, Lisinopril
- Longest acting: Perindopril> Ramipril
  - Ramipril has more $t_{1/2}$
  - Perindopril binds with ACE enzyme with high affinity

Uses of ACE Inhibitors 00:27:52

- DOC for essential HTN
- Used in Hypertension with comorbidity
  - HTN+ Nephropathy (CKD)- Nephroprotective
  - HTN+ Neuropathy/ Stroke- Neuroprotective
  - HTN + Retinopathy- Retinoprotective
  - HTN+Scleroderma-Reduce collagen deposition
  - HTN + DM--Improves glycemic control
- CHF, Post - MI- Cardioprotective

Nephroprotective Effects of ACEI 00:30:26

- Normal mechanism in the kidney:
  - Blood enters glomerulus through afferent arteries
  - Filtered into nephrons
    → Urine is produced
    → This filtration is GFR
  - Some amount of blood goes back through efferent arteries
- In CKD,
  - Hyperfiltration → Leads to albuminuria (hallmark)
- ACE Inhibitors dilate efferent artery
  - GFR is reduced
  - Reduces hyperfiltration injury
  - Reduces risk of albuminuria- Nephroprotective

- In B/L afferent artery stenosis
  - ACE inhibitors are contraindicated
  - They drastically reduce GFR
  → Patient enters into ARF or Oliguria

Contraindications of ACEI 00:35:14

- Bilateral afferent renal artery stenosis
  - Diagnosis: Renal doppler scan
- Hyperkalemia (K^+ >5.5 mEq/L)
- Pregnancy: Risk is maximum in 3rd trimester
  - Aliskiren/Sartans/ Pril—Absolute contraindication
  - Inhibit kidney formation
    → Renal agenesis
  - Category X

Drug Interactions of ACEI 00:38:06

- **Hyperkalemia**
  - Aspirin (NSAIDs)
  - β blockers
  - Cyclosporine
  - Potassium sparing diuretics
- **NSAIDs + ACEI**
  - NSAIDS reduce anti-hypertensive effect of ACEI& reduces blood supply to kidney
    → Increases risk of ARF or oliguria

- Lithium toxicity is increased
  - ACEI increases the reabsorption of lithium
- SULFA drugs and Allopurinol-- Increase the risk of sulfa allergy

Summary-ACE Inhibitor-Side Effects (Mnemonic: CAPTOPRIL) 00:40:30

1. Cough (dry cough)
2. Angioedema
3. Prodrug except (Captopril, Lisnopril)
4. Taste disturbance – captopril
5. Orthostatic hypotension (Decrease BP)
- Seen with ACEI + thiazides : D/t additive hypertensive effect.
6. Pregnancy (Category X)
7. Renal artery stenosis
8. Increase K^+ (Hyperkalemia)
9. Leukopenia/BM Supression by captopril

Angiotensin-1 Receptor Blockers 00:42:44

- E.g., Losartan, Telmisartan
- Angiotensin Receptors: All are G protein coupled receptors (GPCR) PYQ: AIIMS 2019
  - AT-1
    → Gq type
    → Increases IP_3/ DAG
    → Increases BP
    → AT-1 receptors blockers: Sartans
  - AT-2, AT-3 → Gi type → Decreases BP
  - AT-4
    → Present in neurons (CNS)
    → Role in memory and cognition

Drugs in AT-1 Receptor Blockers 00:44:30

- Mnemonic: LOVE TIC
  - Losartan
  - Olmesartan
  - Valsartan
  - Eprosartan
  - Telmisartan
  - Irbesartan
  - Candesartan
  - New drug: Azilsartan
- All are given orally, Not given IV/ injection
  - Not used in hypertensive emergency
- All these drugs are competitive blockers of AT-1 receptor
- Most potent: Candesartan
  - Binds with AT-1 receptor with highest affinity
- Lowest affinity for AT-1: Losartan
- Longest acting: Candesartan> Olmesartan
- Shortest acting: Eprosartan
- All sartan's are excreted in urine & bile
  - Except Telmisartan-Not excreted in urine, it is only excreted in bile
    → Safe in renal disease

Advantage of ARB over ACEI

00:48:22

- Sartan's don't increase bradykinin levels
- ACEI causes increase in Bradykinin levels
  - Causes cough, angioedema

Special Properties of ARB

00:49:15

PYQ: NEET PG 2023

Losartan	• Also block TXA_2 receptor
	  ○ Anti platelet effect
	• Uricosuric action
	  ○ Increased uric acid excretion
	  ○ Good for gout

Irbesartan	• Blocks SA node in heart ○ Effective in atrial fibrillation

Telmisartan	• PPAR-γ agonist (Peroxisomal proliferator activating receptor)
	  ○ Like Pioglitazone
	• Stimulation of PPAR:
	  ○ Insulin sensitivity improves
	  ○ Reduces the risk of T2 DM
	  → By reducing insulin resistance

Sprue with Sartans

- Sartans can cause sprue (Diarrhea d/t malabsorption → weight loss)
- Maximum risk: Olmesartan>others
  - Acts on AT-2 receptors in GIT
    → Inhibitory receptors
    → Reduces absorption of food

29 CALCIUM CHANNEL BLOCKERS

- **MOA -** Block L type of Calcium channels located on the cardiac muscle and smooth muscles of blood vessels.

Types of Calcium Channels	Location	Blockers
L-type	Muscles	CCB
T-type	Neurons - Upon activation cause Absence seizures	Ethosuximide, valproate PYQ: INICET 2022
N-type	Neurons - Increase pain sensation	Ziconotide - Pain killer
P/Q-type	Neurons - Inhibits GABA	Gabapentin, pregabalin

CCB Types

00:03:11

DHP Type

- Also known as dihydropyridine (ends with - dipine)
- Only acts on blood vessels and functions as an artery dilator.
- No direct action on the heart.
- Artery dilatation → Reflex sympathetic discharge → Tachycardia → MI and Angina.
- To prevent reflex tachycardia, dipines are combined with beta-blockers.

Non-DHP Type

- Only two drugs - Diltiazem and verapamil.
- **Diltiazem**
  - Acts on the heart = Blood vessels like arteries.
- **Verapamil**
  - Acts on the heart >>>> Blood vessels.
- Block SA node - Bradycardia
- Block AV node - AV node block
- **Contraindications**
  - Sick sinus syndrome
  - 2°-3° heart block
  - Beta-blockers also block SA and AV nodes - Never combined with verapamil and diltiazem → **Cardiac arrest**.

PYQ: INICET 2022

00:09:10

Verapamil

- **Most cardiac specific CCB** → Blocks SA/AV Node.

PYQ: INICET2020

Use: SVT > Angina > HTN

- **SVT:** Atrial flutter and atrial fibrillation.
  - In SVT - Prevent VT, by blocking AV nodes.
- **Angina:** Inhibit SA node → Decrease HR (decrease oxygen demand)
  - Acts as an artery dilator in HTN.
- Also, block N typed of CCB - Reduces pain like headache (Migraine and cluster headaches)
  - Specific CCB used in migraine headaches - Flunarizine.

Pharmacokinetics

- ROA - Oral, IV
- Inhibit CYP3A4 enzyme → Increases toxicity of other drugs.
- Inhibits P-glycoprotein - Increases Digoxin toxicity.

Side effects

- Vasodilation → Vasodilatory headache.
- Constipation → Relaxes smooth muscles of GIT.

Diltiazem

Most preferred

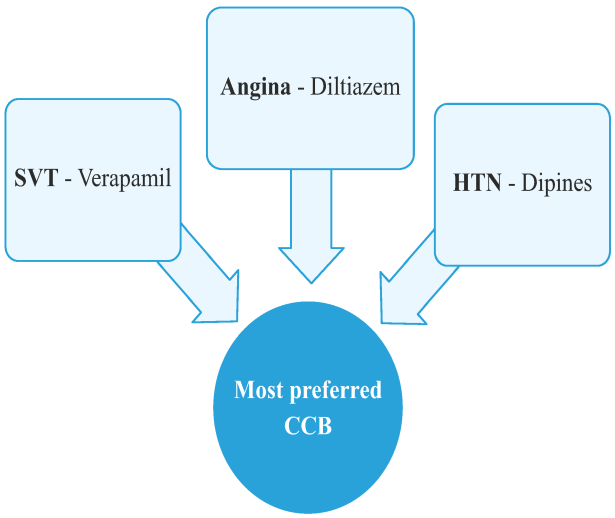
- Angina > HTN > SVT

Mechanism of action

- Inhibit CYP3A4 enzyme

Side effects

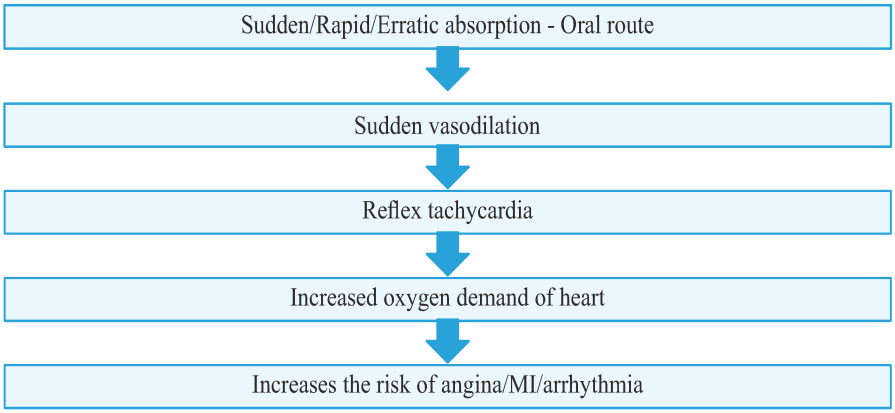
- Vasodilation → Vasodilatory headache
- Constipation → Relaxes smooth muscles of GIT



Dipines (DHP Type) 00:16:16

- Artery dilators
- **Uses**
  - HTN due to artery dilation
  - Peripheral vasodilation (PVD)
  - Raynaud's disease (PVD in fingers)
  - Vasospastic angina
  - Pulmonary artery hypertension

Nifedipine



- Causes paradoxical angina.
- Sustained release oral preparation causes slow and gradual absorption, leading to slow vasodilation and Less risk of causing reflex tachycardia.
- Also, IV and sublingual tablets - Hypertensive emergency.
  - **Side effect:** Drastically reduce the blood pressure → Hypotension.
- Not the first choice of drug in a Hypertensive emergency.

Amlodipine	Longest-acting oral drug
	Least risk of causing reflex tachycardia
	Large volume of distribution
	Liver and renal safe drug
	It does not act on CYP3A4 enzyme - Least drug interaction.
	DOC: Long-term treatment of HTN
Nicardipine	Longest-acting IV drug
	DOC: HTN emergency
Clevidipine	IV shortest-acting CCB
	It enters the blood and gets rapidly degraded by esterase.
	Uses: In HTN emergency along with beta-blockers (To prevent reflex tachycardia)

Important Information

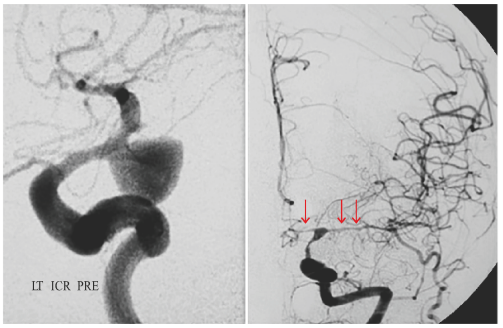
- **Esmolol** - Shortest acting beta-blocker, metabolized by esterase.
- **Clevidipine** - IV shortest-acting CCB

Nimodipine

- Cross meninges or BBB → Cerebral vasodilation.
  - Use: In Mx of cerebral vasospasm in SAH or ICH.
- Cerebro selective CCB.

Due to HTN or Berry Aneurysm, the Meningeal Artery or MMA → **Rupture** → **Haemorrhage** → **Treated by ventricular drain via craniotomy**

- Bleed occurs for two days; after 3 days, bleeding vessels undergo vasospasm → Death in SAH.
- Vasospasm is checked by DSA → >90% mortality rate.



Felodipine	Also, available as a sustained release or extended- release preparation.
Nitrendipine	Increased NO production → Anti-atherosclerotic action.
Others for HTN	Benidipine Isradipine Lercanidipine

- **Note: Mnemonic: H**ypertensives **U**sually **FORGeT** CCB

Side Effects of CCB	**H**eadache- Due to vasodilation in the brain.
	Relax the detrusor muscle → **U**rinary retention.
	Vasodilation in the skin artery → **F**lushing
	Excessive vasodilation → Leakage of plasma → **O**edema (Characteristics of ankle edema)
	Reduce BP/Hypotension
	GERD, as the CCB relaxes LES
	Relaxation of intestinal muscles → **C**onstipation (2nd most common side effect)
	Relax uterus – Nifedipine (**T**ocolytic) → Delays child delivery.

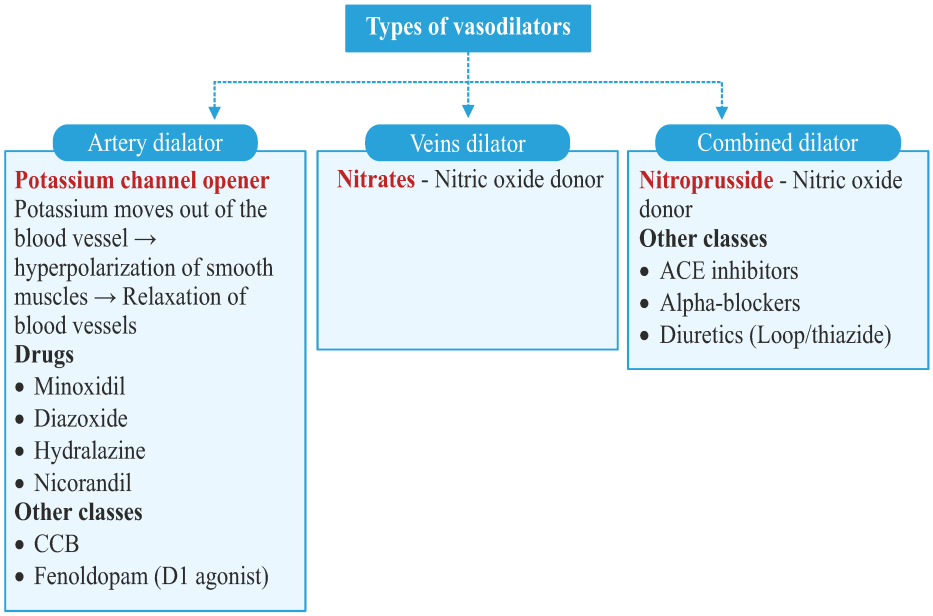
- **CCB toxicity antidote** - Calcium gluconate +/– Insulin → Glucose supply to the heart continues, as CCB suppresses the energy production in the heart.

Advantages of CCB over Beta Blockers

- Beta-blockers are bad as they cause:
  - Bronchoconstriction (Asthma)
  - DM
  - Dyslipidemia
  - PVD, like Raynaud's disease, vasospastic angina
- CCBs are safe in asthmatics, as they do not affect Bronchus, and do not affect DM or dyslipidemia.
  - **DOC:** Raynaud's disease, vasospastic angina.

30 VASODILATORS

- Directly dilate the blood vessels



Common Side Effects of Vasodilators

00:03:45

- **Mnemonic:** FORRR
  - Flushing - Due to vasodilation on the skin
  - Oedema - Due to leakage of plasma
  - Reduce BP (Hypotension)
  - Reflex tachycardia
    → Brain receives less blood supply due to hypotension → Increase BP by sympathetic activity
  - Renin release
    → Sympathetic activity → Acts on the kidney and the latter releases renin

Artery Dilators: Potassium Channel Opener

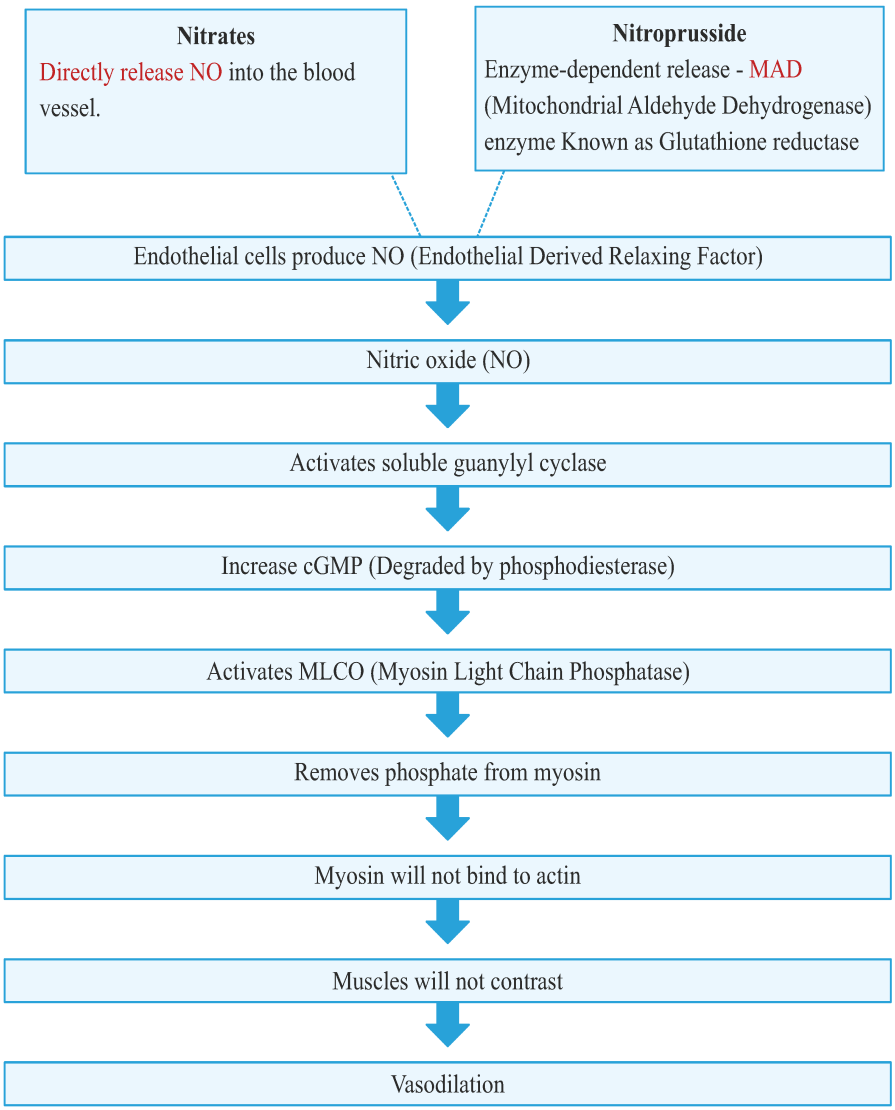
Minoxidil	Prodrug; converted into active form minoxidil sulphate via phase II reaction
	Cutaneous → Hair growth
	Use: Treatment of Alopecia (Topical) combined with finasteride/dutasteride (5-Alpha reductase → Inhibit the conversion of testosterone into DHT)
	Side effects: Oral minoxidil → Hirsutism in females
Diazoxide	Opens potassium channels on beta cells of the pancreas → Hyperpolarization → inhibits insulin secretion
	Use: Treatment of insulinoma tumors
	Side effects: Hypoglycemia
	Contraindications: DM

Hydralazine	MOA
	Potassium channel opener
	Antioxidant properties
	Nitric oxide donor
	Uses: • HTN • HF → Cardioprotectic effect due to antioxidant properties
	Side effects: Sulfonamides Hydralazine Isoniazid Procainamide (SHIP) drugs undergo acetylation → DLE

Nitric Oxide Donor

00:10:58

Mechanism of action



Nitrates with PDE Inhibitors

00:15:43

- Nitrates are used in angina and MI in old age.
- PDE inhibitors for impotence or erectile dysfunction - Sildenafil and Tadalafil.
- **Nitrates:** ↑ NO → ↑ cGMP→ Vasodilation.
- **PDE Inhibitors:** Inhibits degradation of cGMP- ↑ cGMP→ Vasodilation.
- Nitrates with PDE Inhibitors → ↑ Massive vasodilation → Hypotension → Sudden death.
- A Gap is maintained between administering these drugs
  - Nitrates ⇔ Sildenafil: 24 hours
  - Nitrates ⇔ Tadalafil: 72 hours

Difference Between Nitroprusside and Nitrates

00:18:38

Nitroprusside	Nitrates
Direct NO donor	Enzyme-dependent NO donor - MAD enzyme
Combined dilator	Vasodilators - MAD is present only in veins
No tolerance	Show tolerance (If continuously given → Downregulation of MAD enzyme → Loss of effect)

Nitroprusside

00:20:47

- Only IV drug
- Fastest-acting antihypertensive drug → Action ~30 seconds
- Used in hypertensive emergencies

Side effects

Cyanide toxicity
- Nitroprusside → liver → converted into cyanide → hypoxia

Thiocyanate toxicity
- Hypothyroidism, as it inhibits the entry of iodine into the thyroid gland → Decreases T3, T4

Photo volatile – Degrades in light
- Always stored in a dark-colored or amber colored bottle
- The drip is always covered with black paper

Cyanide Toxicity

00:23:30

Mechanism

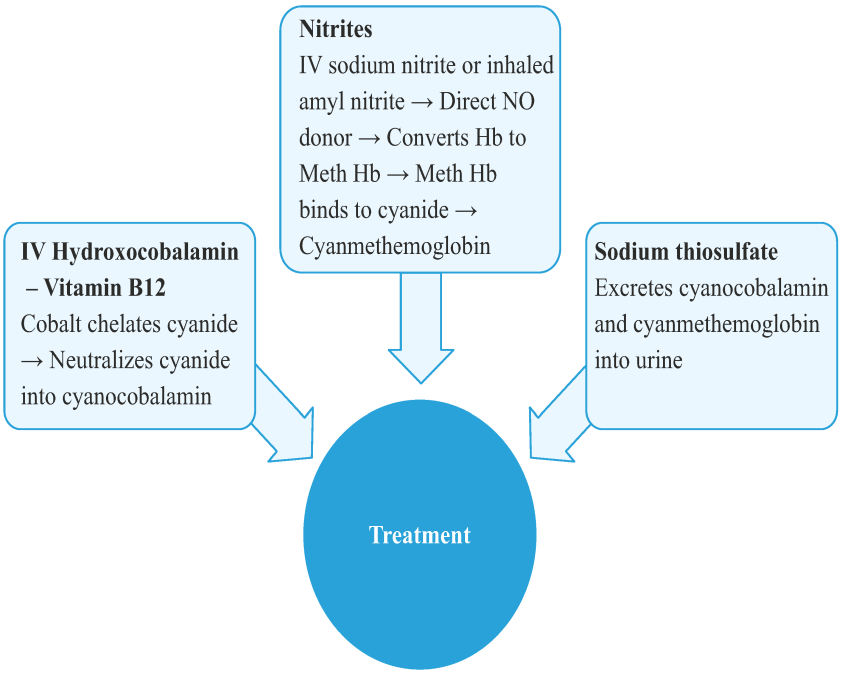
CN enters cells

↓

Binds with cytochrome C (utilisation of oxygen, which further converts to ATP)

↓

Histotoxic hypoxia



- Given in combination, sometimes three drugs come in a kit called a cyanide kit.

31 ANTI ANGINAL DRUGS

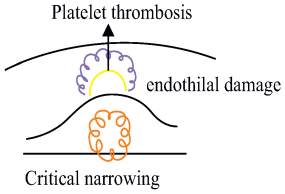
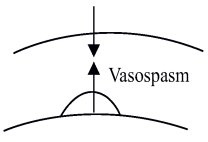
Angina

- Ischemic pain in heart due to coronary artery blockage
- Manifestations
  - Chest pain
  - Radiates to arm and back
  - Sympathetic symptoms: Sweating, tremors

Types of Angina

Medicine 00:01:28

- Divided into three types

Stable angina (mc)	**Unstable angina**	**Prinzmetal angina**
k/a Classical Angina k/a Exertional Angina	↓ "Acute Coronary syndrome" (MI)	k/a Vasospastic Angina k/a Variant Angina
• Narrowing of the coronary artery due to atherosclerosis below the endothelial cells • But still, >30% is open, which is sufficient to meet the demand of the heart at rest	• Increased speed of blood due to atherosclerosis leads to endothelial damage • There is platelet aggregation forming a thrombus • Results in critical narrowing	• There is sudden vasospasm due to endothelial dysfunction • Leads to complete blockage
 Atherosclerosis	 Critical narrowing	 Endothelial dysfunction
Clinical features: Normal at rest ↓ Exertion: Increased O_2 demand ↓ Anginal pain	↓ Managed as MI Aspirin (Antiplatelet)	↓ Pain at Rest

- DOC for acute angina- Sublingual nitrates
  - Nitroglycerin- 0.5 mg
  - Isosorbide dinitrate- 5 mg
- DOC for chronic angina
  - Chronic stable angina- β blockers
    - → Decrease heart rate and oxygen demand
    - → Still not controlled- Add calcium channel blockers
    - → Still not controlled- Add nitrates
      - ROA- Oral, transdermal patches
    - → Aspirin- Prophylactic treatment
  - Chronic Vasospastic angina
    - → DOC- Calcium channel blockers DHP type

→ Long acting nitrates- Oral, transdermal patches
→ Contraindication- β blockers (produce vasoconstriction)

Drugs for Chronic Angina

00:09:46

First line drugs	• Beta blockers • Calcium channel blockers • Nitrates
Second line drugs	• Treat resistant angina • **Mnemonic-** No DRIFT ○ **No-** Nicorandil ○ **D-** Dipyridamole (Not used in angina) → Cause- Coronary steal Syndrome ○ **R-** Ranolazine (Became 1st line drug) ○ **I-** Ivabradine ○ **F-** Fasudil ○ **T-** Trimetazidine

First Line Drugs

00:12:12

1. β blockers

- MOA

Blocks β 1 receptor on myocardium
↓
Decreases the heart rate
↓
Decrease in oxygen demand

Side effects

- Blocks β 2 receptors on coronary arteries- Increased risk of vasoconstriction
- Increase the risk of Vasospastic angina

Types

- Divided into two types

Cardioselective β blocker	• Blocks β 1 receptor than β 2 • Mainly preferred • **Mnemonic-** MAN B ○ Metoprolol ○ Atenolol ○ Nebivolol ○ Bisoprolol
Non selective β blockers	• Blocks β 1 and β 2 receptors equally • Drug- Propranolol ○ Contraindications- Vasospastic angina

2. Calcium channel blockers

DHP types (Dipine)	• It include drugs like
	  ○ Amlodipine
	  ○ Nifedipine
	  ○ Felodipine
	• MOA- Coronary artery dilator
	• DOC- Chronic Vasospastic angina
	• Side effects- Reflex tachycardia
	  ○ Increase in oxygen demand
	  → Increase risk of stable angina
	• Combined with β blockers
	  ○ Prevent tachycardia

Non DHP types	• It includes
	  ○ Verapamil
	  ○ Diltiazem
	• Acts both on heart and coronary artery
	• MOA- Decrease heart → decrease O_2 demand
	• Uses
	  ○ Stable angina
	  ○ Coronary dilator
	  ○ Vasospastic angina
	• Never combined with β blockers
	  ○ Marked bradycardia

- Contraindications- Right ventricular failure
  - ○ Increase preload (IV fluids)

3. Nitrates

- Other Name- Organic nitrates, Non ionic drugs
- MOA- Venodilators

Reduce preload
↓
Reduce myocardial contractility
↓
Decreased O_2 demand

- Other beneficial effects :

Nitrates
↓
Nitric oxide
↓
Dilates coronary artery
↓
Effective in vasospastic angina

- Nitrates- Redistribution of coronary blood flow
  - ○ Non ischemic area to ischemic area
  - ○ Other Name- Robinhood phenomenon
    → Nitrates
    → β blockers

Nitrate drugs	Route
Glyceryl trinitrate (Nitroglycerin)	• Oral, sublingual, transdermal, rectal, nasal spray, IV • Not given as subcutaneous, intramuscular injection
Isosorbide dinitrate	• Oral, sublingual
Isosorbide mononitrate	• Oral only
Pentaerythritol nitrate	

- Chemical nature- Highly lipid soluble
- First pass metabolism in liver- Oral (High first pass metabolism)
  - To avoid FPM - Rectal, sublingual
  - Isosorbide mononitrate doesn't have first pass metabolism (100% oral bioavailability)
- Prodrug- Isosorbide dinitrate
  - Isosorbide dinitrate → Isosorbide mononitrate (Active form)
- Shortest acting: Sublingual glyceryl trinitrate
- Longest acting: Pentaerythritol tetranitrate
- Older days- Inhalational Amyl nitrate for angina
  - Recommended in cyanide poisoning

Uses

- Angina-
  - Stable, Vasospastic angina
  - Acute, chronic angina
- Myocardial infarction or acute coronary syndrome: Three types

Unstable angina **NSTEMI**	• Initial management: Mnemonic- MONA o Morphine- Chest pain relief o Oxygen o Nitroglycerin o Aspirin- Antiplatelet drug
STEMI	• **Mnemonic**- MONAS o Morphine- Chest pain relief o Oxygen o Nitroglycerin o Aspirin- Antiplatelet drug o Streptokinase or other thrombolytics

- Acute LVF/Pulmonary edema
  - Reduce preload
  - Drugs- Venodilators
    - → L- Loop diuretics
    - → M-Morphine
    - → N-Nitroglycerin

- To treat abdominal colicky pain
  - Biliary colic
  - Esophageal colic
    → Relax GIT muscles
  - Not recommended in renal colic

Drug interactions

Nitrates
↓
Donate nitric oxide with the help of mitochondrial aldehyde dehydrogenase (MAD) enzyme
↓
Activate soluble guanylyl cyclase enzyme
↓
Increase in cyclic GMP (degraded by phosphodiesterase enzyme)
↓
Vasodilation

- PDE 5 inhibitors- Causes vasodilation
  - Sildenafil
  - Tadalafil
  - Not combined with the nitrates
    → Causes massive vasodilation
      - Hypotension
      - Sudden death
- Gap between sildenafil and nitrates- 24 hrs
- Gap between tadalafil and nitrates- 72 hrs

Adverse effects and contraindications

Adverse effects	Contraindications
Hypotension Flushing Edema	SBP < 90 mmHg
Reflex tachycardia	HR >100 BPM
Bradycardia (Bezald Zarich reflex)	HR<50 BPM

Nitrates in LVF and RVF

- Used to treat LVF
  - To reduce preload
- Absolute contraindicated in RVF
  - Preload has to be increased
  - Treatment: IV fluids

Nitrate Tolerance

- Other Name- Mondays disease
- Reduced effect with time
- Long acting route- Down regulation of MAD enzymes

- Treatment- Nitrate free interval of 8 hrs (During night)
  - Regeneration of MAD enzymes
- Molsidomine- Direct nitric oxide donor
  - Does not show tolerance

Second Line Anti-Anginal Drugs

00:41:42

- **Mnemonic-** No DRIFT
  - No- Nicorandil
  - D- Dipyridamole
  - R- Ranolazine
  - I- Ivabradine
  - F- Fasudil
  - T- Trimetazidine

1. Nicorandil

- MOA- Potassium channel opener
  - Causes coronary dilation
  - Has antioxidant action - protects the heart
  - Produce ischemic preconditioning- Makes the heart resistant to ischemia
- Uses- Resistant angina
- Side effects- Mouth or GIT ulcers (Aphthous ulcers)

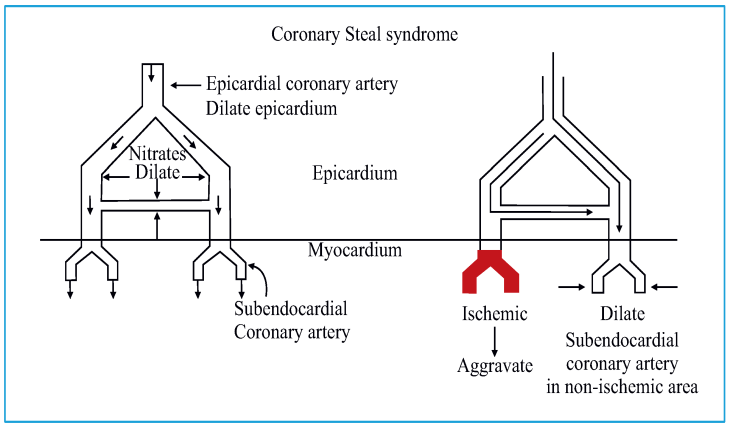
2. Dipyridamole

MOA

PDE 3 inhibitor
↓
Accumulation of adenosine
↓
Adenosine efflux
↓
Coronary dilator

- It dilates coronary artery in non-ischemic area (Rich area)
  - Diverts the blood from the ischemic area with poor blood supply to the non-ischemic area
  - Other Name- Coronary steal syndrome, Reverse Robinhood phenomenon

Coronary steal syndrome



- Epicardium- Surface of heart
- Coronary artery- Epicardial coronary artery
- Sub endocardial coronary artery- Below the myocardium

Ischemic area

↓

Dipyridamole like drugs dilate the subendocardial coronary artery in non-ischemic area

↓

Aggravation of ischemia

↓

Worsening of the angina symptoms

- Nitrates - Dilate epicardial coronary artery and increase the blood supply to the ischemic area

Drugs causing coronary steal syndrome

- Mnemonic- HIND
  - H- Hydralazine
  - I- Isoflurane (General anesthetic)
  - – Nitroprusside
  - D- Dipyridamole

3. Ranolazine

- MOA- Blocks sodium channels on myocardium
  - Reduced myocardial workload (Decreased O_2 demand)
- 1st line drug for chronic stable angina
- Treat ventricular tachycardia
- Minor action- PFOX inhibitor
- Uses
  - Improves glycemic control
    → Decrease HbA1c levels
    → Blocks K^+ channels in pancreas
    – Increase in insulin secretion
- Side effects- QT Prolongation
  - Blocks K^+ channels in heart

4. Fasudil

- Rho kinase enzyme inhibitor
  - Other Name- Rock enzyme
  - Coronary dilator
- Use- Chronic vasospastic angina

5. Trimetazidine

- MOA- Partial fatty acid oxidation inhibitor
  - Inhibit thiolase enzyme
- Fatty acids (Heart) + O_2 (More) → ATP ↑
- Glucose + O_2 (Less)→ ATP ↑
- Heart shift the fuel metabolism from fatty acids to glucose
- Side effect- Causes parkinson disease
  - Increases the degradation of dopamine

6. Ivabradine

- MOA- Inhibit funny channels on SA node
  - Other Name- IF current
  - Reduce heart rate/ Bradycardia (Decreased O_2 demand)
- Use-
  - Chronic stable angina
  - Chronic heart failure
- Side effects
  - Visual abnormality
    - → Blocks funny channels on retina
      - – Luminous phenomenon (normal light appears excessively bright)
- Ivabradine
  - I- Inhibit funny channels
  - VA- Visual abnormality
  - Bradine- Bradycardia

32 HYPOLIPIDEMIC DRUGS

- Also called antihyperlipidemic drugs
- High blood lipids: Dyslipidemia

Lipids

Cyclical lipid (Cholesterol)

- This leads to atherosclerosis (deposition and narrowing of blood vessels)
- In Coronary artery – MI
- In Cerebral artery - Stroke
- Deposition in skin - Xanthomas

Straight-chain lipid (Triglycerides)

- High levels damage the pancreas
- Causes acute pancreatitis

Physiology of Lipids — **Biochemistry** — 00:02:42

Food having high triglycerides and cholesterol

↓

Absorbed into lymph (water media)

↓

Lipoproteins (chylomicron) transport lipids in lymph

↓

Chylomicrons travel to the liver

↓

Gets absorbed

↓

Liver secretes VLDL in blood-Transports both triglycerides and cholesterol

↓

LPL (Lipoprotein lipase) enzyme present on endothelial cells in blood vessels

↓

Removes triglycerides

↓

VLDL converted to IDL (cholesterol > triglycerides)

↓

IDL is converted to LDL (contains only cholesterol)

- If body cells (contain LDL receptors) require cholesterol LDL donates cholesterol to body cells

Bad Lipids

- Chylomicrons
- VLDL
- IDL
- LDL

Good Lipid

- HDL
  - Removes cholesterol from body cells by transferring cholesterol back to LDL by cholesterylester transfer protein enzyme and LDL is removed by the liver
  - High levels reduce the risk of atherosclerosis

Hypolipidemic Drugs

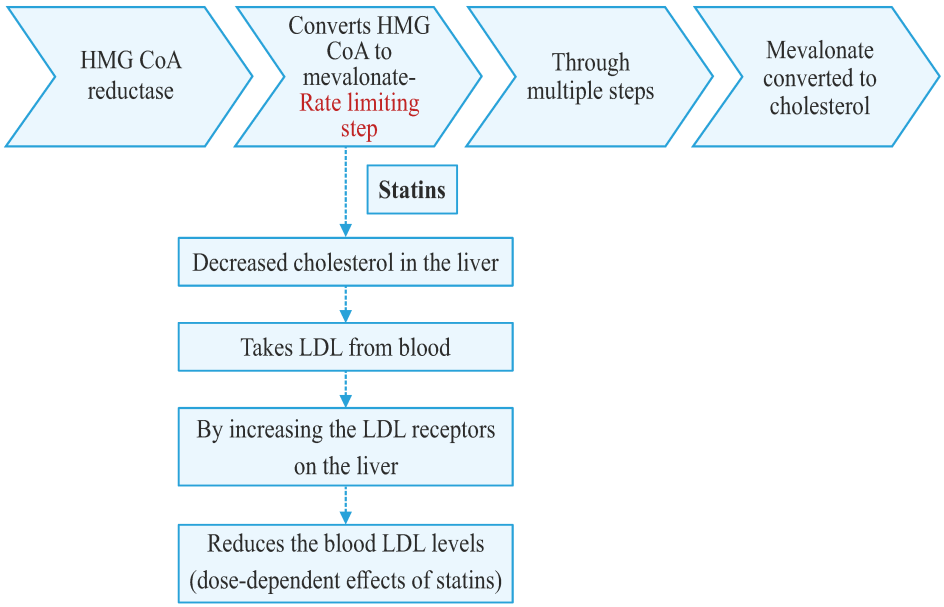
00:08:46

Statins

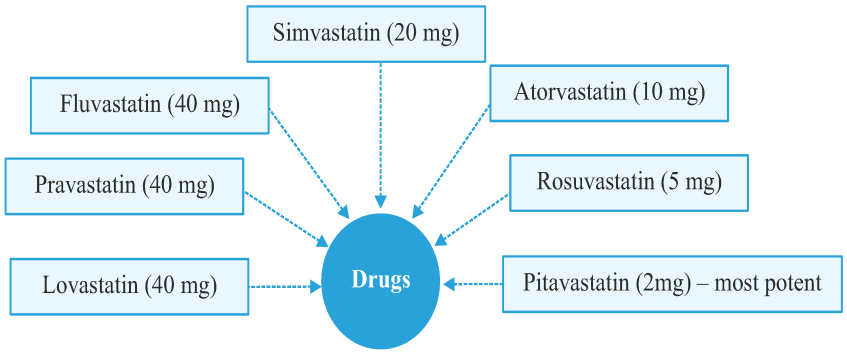
- Inhibit the synthesis of cholesterol inside the liver

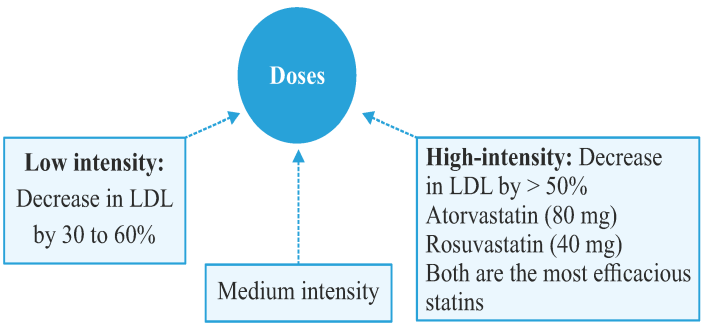
Mechanism of action:

- Competitive inhibitor of HMG-CoA reductase



- Increases HDL levels
- Decreases triglycerides levels





Uses of statins

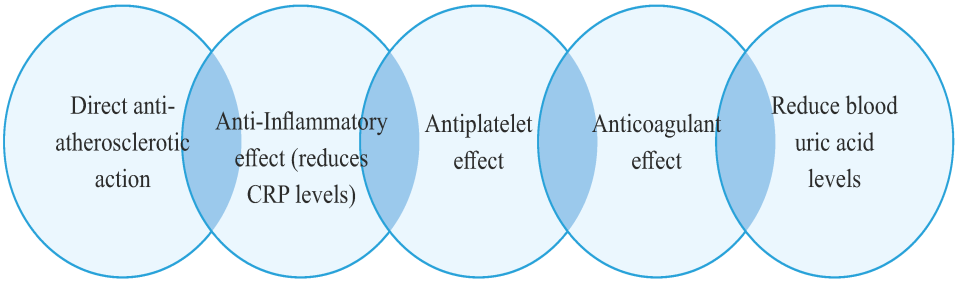
DOC for hypercholesterolemia

- Leads to atherosclerosis, causing MI or stroke
- Causes of hypercholesterolemia:
  - Drug induced
    → Loop and thiazide diuretics
    → Glucocorticoids
  - Genetic cause - Familial type 2 hyperlipidemia
  - Metabolic syndrome

High-intensity statins

- MI and stroke
- LDL >190 mg/dl (Target < 100 mg/dl
- Raised LDL with diabetes mellitus

Pleiotropic effects



Pharmacokinetics

- Oral, injection (Atorvastatin and rosuvastatin)
- Most potent: Pitavastatin
- Most efficacious: Rosuvastatin > Atorvastatin
- Longest acting: Rosuvastatin > Atorvastatin
- Given during the night before sleep except for rosuvastatin and atorvastatin (can be taken at any time)
- Metabolized by CYP3A4 enzyme producing a lot of drug interaction
  - Exceptions
    → Fluvastatin (metabolized by CYP2C9 enzyme)
    → Rosuvastatin
    → Pravastatin

Important Information
Most effective and least drug interactions seen with Rosuvastatin

Side effects

- Hepatotoxicity
- Myopathy

Myopathy

Pathophysiology

Caused by decreased production of coenzyme QA (helps in muscle function) due to HMG CoA reductase

Features

- Muscle pain
- Sometimes causes rhabdomyolysis

Rhabdomyolysis

- Substances present in muscles come into the blood
- Leads to
  - Lactic acidosis
  - Hyperkalemia
  - Myoglobinuria (cola-colored urine) – Leads to ARF

Causes of increased risk of myopathy with statin

- High-intensity or high-dose statins
- Alcoholics
- CYP enzyme inhibitors-erythromycin, ketoconazole
- Female gender
- Combination of statin with other hypolipidemic drugs like niacin, fibrates

Cola colored urine

Contraindications

- Pregnancy (category X drugs)
- Children <12 years of age
- Pravastatin contraindicated in children < 8 years of age

Resins

00:29:14

- Also called Bile acid binders (sequestrants)

Liver releases Bile
↓
Enters the intestine
↓
95% of the bile gets reabsorbed into liver
↓
Resin binds to bile acid in GIT
↓
Inhibits reabsorption of bile into liver (enterohepatic reabsorption of bile)
↓
No cholesterol in liver
↓
For compensation increases LDL receptors in liver
↓
Reduces LDL in blood

Drugs	• Cholestyramine (powder) • Colestipol (powder) • Colesevelam (tablet)
Uses	• DOC to reduce blood cholesterol in pregnancy • Add on drug to statins • Colesevelam -Approved for Type 2 DM • Sometimes given in treatment of hyperthyroidism • Sometimes used to control pruritus in CLD
Side effects	• Malabsorption of fat soluble vitamins • Reduce absorption of Digoxin, propranolol and thyroxine

Fibrates

00:34:50

PYQ: INICET 2022

- Also called lipoprotein lipase activators

Blood vessels

↓

Endothelial cells are present

↓

Nucleus contains PPAR (peroxisomal proliferator activating) α receptors

↓

Fibrates stimulate PPAR α receptors

↓

LPL enzyme is synthesized on surface of endothelial cells

↓

Removes triglycerides from blood

Uses

- DOC for hypertriglyceridemia
- Causes of hypertriglyceridemia
  - Alcohol
  - Diabetes mellitus
  - Familial hyperlipidemia type 3: Dysbetalipoproteinemia

Drugs

PYQ: FMGE 2023

- **Clofibrate**: Banned as it was increasing LDL
- **Fenofibrate**
  - No CYP action
  - Safely combined with statins
- **Bezafibrate**: Least risk of causing myopathy
- **Gemfibrozil**: CYP inhibitor
  - Increase statin levels
  - Shouldn't be combined with statins

Side effects

- Myopathy
- Gallstones

Important Information

- Statins should be taken after a meal
- Fibrates should be taken before a meal

Niacin

00:40:18

- Nicotinic acid (vitamin B3)
- **High dose -** Hypolipidemic effect
- **Dose:** 2 to 6 grams

Mechanism of action

In liver

- Decreases triglyceride synthesis
- Increases HDL
- Decreases lipoprotein (a) levels (Marker of atherosclerosis)

In adipose tissue

- Inhibits lipolysis
- Decreases triglyceride synthesis

- Most toxic drug as it is given in high doses
- Used in resistant cases resistant to
  - Statins
  - Fibrates
- Given as add-on drugs
- Specifically used to increase HDL levels

Side effects

- **Flushing**
  - Due to increased PG D_2 synthesis by Niacin
  - Causes cutaneous vasodilation
  - Treatment:
    - → Aspirin (inhibits COX enzyme)
    - → Laropiprant - New drug (PG D_2 receptor antagonist)
- Hepatotoxicity
- Hyperuricemia (avoid Niacin in gout)
- Hyperpigmentation on skin

Flushing

Important Information

Hypolipidemic drugs do not have acute pancreatitis as a side effect

Hypolipidemic effect on uric acid

- Reduced by
  - Statins
  - Fibrates
  - Good for gout
- Increased by
  - Niacin
  - Bad for gout

Hypolipidemic effect on diabetes mellitus

- Niacin and statins
  - Cause hyperglycemia
  - Increase the risk of Type 2 DM

Drugs	LDL-C	Total TG	HDL	Point to be noted
Statins	Decreases (maximum- 50%)	Mild reduction	Increases	DOC for hypercholesterolemia
Resin	Decreases	Increases	No effect	DOC in pregnancy
Fibrates	Decreases	Maximum reduction (50%)	Increases	DOC for hypertriglyceridemia
Niacin	Decreases	Reduces (almost near to 50%)	Maximum increase	Reduce lipoprotein (a) levels

Target blood lipid levels

HDL > 50	LDL < 100
Triglycerides <150	Total cholesterol <200

- Above or below target values: DOC is statins
- If TGs > 350: statins + fibrates

New Hypolipidemic Drugs

00:51:30

- Ezetimibe
- PCSK 9 inhibitors
- Lomitapide
- Omega 3 fatty acids
- Bempedoic acid

Ezetimibe

- Inhibits NPC_1L_1
  - Present in intestine
  - Helps in cholesterol absorption from intestine
- Hence inhibits cholesterol absorption from intestine
- Add on drug to statins
- Reduce LDL levels

PCSK 9 inhibitors

PYQ: NEET PG 2022

- Drugs
  - Evolocumab, Alirocumab } Injection
  - Inclisiran (new drug): Silencing RNA
- PCSK 9 enzyme degrades LDL receptor on liver
- If blocked – More LDL receptors on liver
- Hence reduce blood LDL levels
- Given in cases resistant to
- They are expensive drugs

Lomitapide

- MTP inhibitor (Microsomal triglyceride transfer protein): Synthesizes and secretes VLDL
- If it is inhibited VLDL levels are decreased

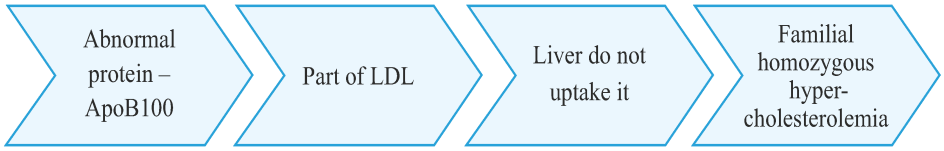
Omega 3 fatty acids

- Present in fish
- Decrease VLDL production in liver
- Drugs
  - Eicosa penta enoic acid (Icosapent)
  - Docosa hexa enoic acid
- New drug: Bempedoic acid
  - Inhibits ATP citrate lyase enzyme required to convert ATP citrate to HMG CoA
- Add on drug to statins
- Reduces LDL

Rare Drugs

00:59:30

- **Mipomersen**
  - RNA anti- sense strand
  - Inhibits mRNA translation
  - Decrease abnormal protein production



- **Anacetrapib and Torcetrapib**
  - CETP inhibitors
  - Increases HDL levels
  - Increased risk of MI
    → HDL action is decreased

33 HYPERTENSION

Definition of Hypertension

00:00:28

- Sustained elevation of BP that increases the risk of organ damage (comorbidity)

American Heart Association (AHA) guidelines for Hypertension

Blood pressure category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	**And**	<80
Elevated	120-129	**And**	<80
HTN stage 1	130-139	**Or**	80-89
HTN stage 2	>140	**Or**	>90
Hypertensive crisis	>180	**Or**	>120

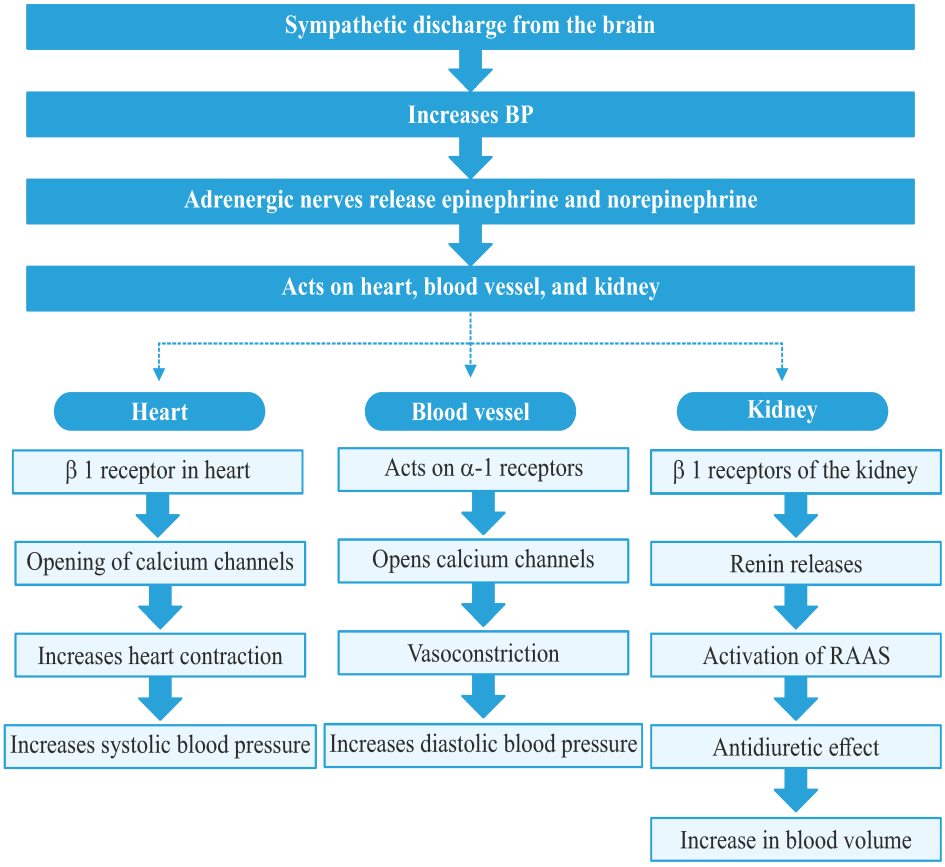
- Earlier, stage 2 hypertension was known as stage 1 hypertension.
- Anti-hypertensive drugs are started in case of hypertension and in case of elevated BP lifestyle modifications (low sodium diet) are advised.
- Target BP: 120/80 mmHg

Pathophysiology of Hypertension

Physiology

00:03:55

PYQ: FMGE 2023



Classification of Antihypertensives

00:06:45

Sympatholytics

- Reduces sympathetic activity by stimulation of α-2 receptors in the brain

Centrally acting sympatholytic drugs
- Clonidine
- α methylodopa
  - Produce all actions

Adrenergic neuron blockers
- Reserpine
- Guanethidine
  - Not in use as they cause severe hypotension

β-blockers
- Acts on heart-Decreases CO
- Acts on kidney- Decreases renin release

α-blockers
- Produce vasodilation

Diuretics

- Thiazides
- Loop diuretics
- Potassium-sparing diuretics-Spironolactone, Eplerenone

RAAS inhibitors

- ACE inhibitors (pril)
- ARB
- Aliskiren

Calcium channel blockers

- DHP
- Non-DHP

Vasodilators

- Direct vasodilators

Choice of Antihypertensives

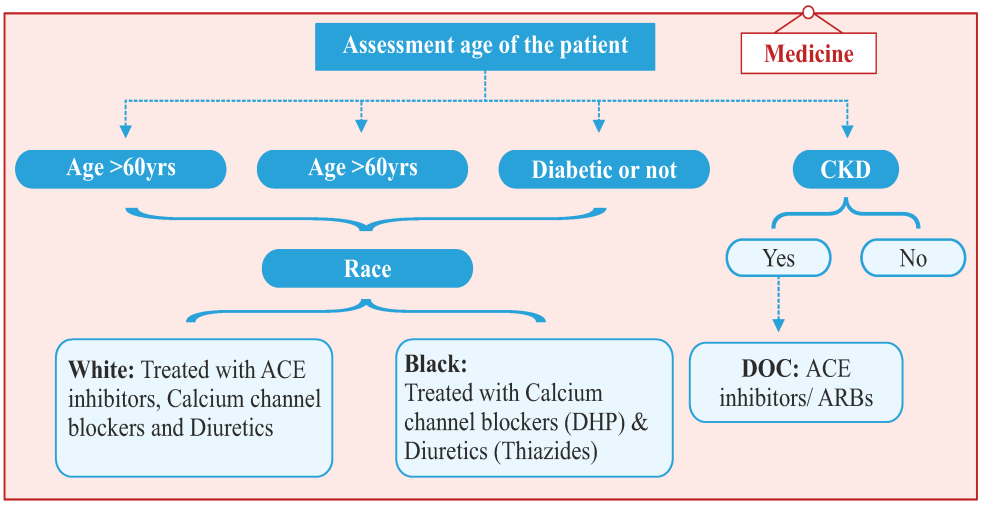
Essential hypertension

00:13:10

PYQ: NEET PG 2021

- Also known as primary or idiopathic HTN
- Most common type of HTN
- Risk factor: High salt diet
- Lifestyle modification: Low salt diet
- **1st line Drugs**
  - ACE inhibitors/ AT1 receptor blockers
    → Ends with Pril/ Sartan
  - Calcium channel blockers: DHP type
    → Ends with Dipine
  - Diuretics: Thiazides

- β-blockers: 2nd Line Drugs
- JNC (Joint National Committee) 8 guidelines



- Target BP for >60 year old individuals: <150/90 mmHg
- In all other conditions: at least <140/90 mmHg

Uncontrolled HTN	Resistance HTN	Refractory HTN
• BP is not controlled by 2 drugs at a maximum tolerable dose • Treatment: add 3rd drug	• BP not controlled by 3 drugs (one of which should be a diuretic) at maximum tolerable dose • Treatment: Add Spironolactone/ Eplerenone (Aldosterone receptor antagonists)	• BP is not controlled by 5 drugs together (including a long acting thiazide-like diuretic and a mineralocorticoid receptor antagonist) at a maximum tolerable dose • Treatment: removal of sympathetic nerves from kidney and other organs ○ Sympathectomy

Hypertension with comorbidity

00:21:10

PYQ: FMGE 2023

DOC: ACE inhibitors (pril) • CKD, Microalbuminuria, ESRD • Diabetes mellitus • Metabolic syndrome (obesity) • Stroke • Retinopathy • Scleroderma	**COD: CCB – DHP type (Dipine)** • Peripheral vascular disease • Renal artery stenosis • Atherosclerosis • Isolated systolic hypertension	**DOC is β – blockers** • Stable angina • HOCM • Aortic dissection • Atrial fibrillation • Migraine • Hyperthyroidism
Benign prostatic hypertrophy • DOC: Prazosin (α 1 blocker) – Relaxes urinary sphincter	**Osteoporosis** • DOC: Thiazide diuretics • Preserve calcium from urine • Blood calcium increases bone mineral density	**Postmenopausal Hot flushes** • DOC: Clonidine

Hyperaldosteronism	Pheochromocytoma	Cheese reaction, Clonidine sudden withdrawal
• DOC: Spironolactone or Eplerenone	• DOC: Phenoxybenzamine (α-blocker)	• DOC: Phentolamine

Important Information

- In asthmatics having angina, HOCM, or aortic dissection: CCB non-DHP type (Verapamil or Diltiazem)

Condition	Drugs Contraindicated
Gout	Loop & Thiazide diuretics
• Hyperkalemia • Renal artery stenosis • Pregnancy • Angioneurotic edema	ACE inhibitors/ AT1 receptor blockers
• Hyperkalemia • Serum creatinine >2.5 mg/dL in men (Renal disease)	Spironolactone
• Asthma/COPD	β-blockers
• Bradycardia • AV node block	β blockers, Verapamil & Diltiazem

Hypertension in pregnancy 00:27:17

Safe drugs	Unsafe drugs
• Mnemonic: LHMC PYQ: NEET PG 2021 PYQ: FMGE 2021 ○ Labetalol – DOC ○ Hydralazine ○ Methyldopa ○ CCB like Nifedipine	• Mnemonic: SAAND ○ Spironolactone ○ ACE inhibitors/AT1 receptor blockers → Inhibits RAAS system – Renal agenesis ○ Atenolol → Causes placental ischemia ○ Nitroprusside → Leads to cyanide toxicity ○ Diuretics → Loop and Thiazides → Causes placental ischemia

Chronic HTN in pregnancy

- **DOC: α Methyldopa (safest)**
- Labetalol

PYQ: FMGE 2023

Pregnancy induced HTN

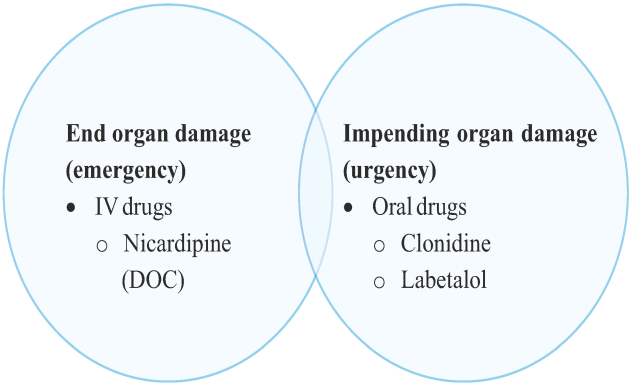
- Placental changes >20 weeks of gestation
- Preeclampsia: leads to organ damage
  - Retinal damage: blindness
  - Kidney: albuminuria
- Seizures: Eclampsia
- **DOC: Labetalol oral or IV**
  - Can add Nifedipine (sublingual)
  - Hydralazine IV

- Overall, DOC: Labetalol, but contraindicated in Asthma

Hypertensive Crisis

00:33:18

- BP: >180/120 mmHg



- Patient has
  - Stroke
  - MI
  - Aortic dissection
  - Kidney damage or ARF

- Malignant HTN
  - The sudden elevation of BP
  - IV drugs are given

Drugs for hypertensive emergency	Drugs not used in hypertensive emergency
• Now – Nicardipine (DOC) • **Nobody** – Nitroprusside • **C** – Clonidine • **A** – ACEI: Enalaprilat IV • **N:** Nitrates, Nifedipine • **H:** Hydralazine • **E:** Esmolol, Labetalol • **L:** Loop diuretics • **P:** Phenoxybenzamine • **U:** Urapidil (α 1 blocker) **Finally:** Fenoldapam (D1 receptors agonist)	• Thiazides ○ Not effective in severe HTN • AT1 receptor blockers (Sartan)

34 DRUGS FOR HEART FAILURE

Heart Failure

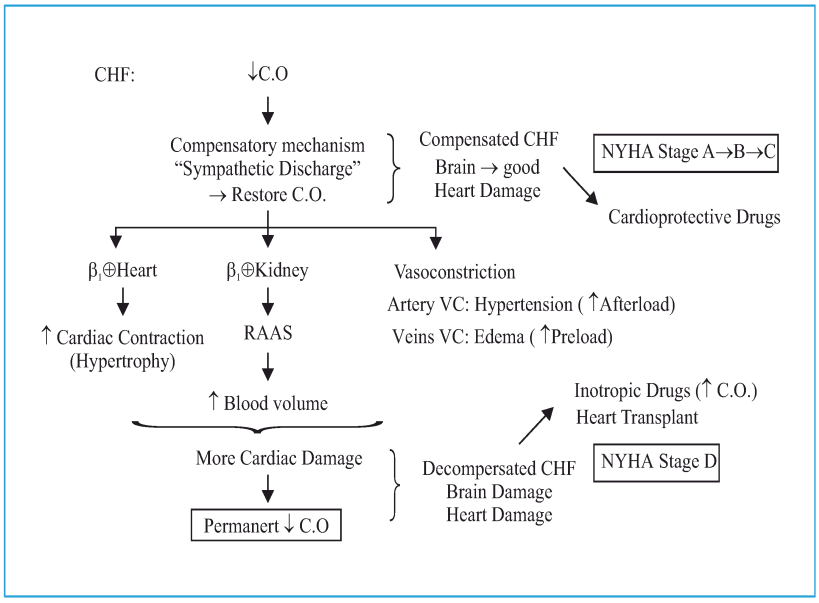
00:00:03

- **In heart failure -** Heart is unable to pump sufficient amount of blood that meets the demands of peripheral organ

- **2 types**
  - Low output HF
    - → There is damage to the heart
    - → Decreased supply (decrease in CO)
    - → MC cause: Myocardial infarction
  - High output HF
    - → No damage to the heart
    - → Increased demand of peripheral organs
    - → Has various causes: Anemia, beriberi, AV malformations, etc
    - → Treatment: Treat the cause

Low Output Heart Failure

Physiology 00:03:00



- **Sympathetic discharge:** Epinephrine and norepinephrine
  - Activates β 1 receptor on heart
    - → Leads to cardiac contraction
    - → Causes hypertrophy
  - Activates β 1 receptor on kidneys
    - → Activates RAAS
    - → Increases blood volume
    - → More CO

- Causes vasoconstriction
  - → **Artery vasoconstriction**
    - Leads to hypertension
    - Increase in afterload
  - → **Veins vasoconstriction**
    - Leads to edema
    - Increase in preload

- **Compensated CHF**
  - Brain is normal
  - Heart is damaged
  - Treated with cardioprotective drugs
    - → β blockers
    - → RAAS inhibitors
    - → Vasodilators

- **Decompensated CHF**
  - First brain is protected
  - Treated with Inotropic drugs- Increase CO
  - Heart can't be saved
  - Heart transplantation is the only choice

Drugs for CHF

00:10:49

- **Cardioprotective drugs**

PYQ: FMGE 2020, 2022

  - Reduce cardiac hypertrophy (cardiac remodelling)
  - Only drugs that increase lifespan of a person

- **Symptomatic relief**
  - **Aim:** To reduce
    - → Preload (treatment of pedal edema)
    - → Afterload (treatment of HTN)
  - No mortality benefit
  - **Drugs**
    - → Loop/ thiazide diuretics
    - → Vasodilators
    - → Nitrates
    - → Natriuretic peptides

- **Inotropic drugs**
  - Increase CO by increasing force of contraction
  - Treatment of Decompensated HF
  - No mortality benefits
  - Increase cardiac mortality
  - **Drug:** Digoxin

01. Cardioprotective Drugs

00:14:26

- **Drugs (Mnemonic: SAHIBS)**
  - Sacubitril
  - ACE inhibitor or ARB
  - Aldosterone antagonist
    - → Spironolactone
    - → Eplerenone
  - Hydralazine (artery dilator) + ISDN (vein dilator) - Bidil
  - Ivabradine
  - β blockers
  - **SGLT-2 inhibitors**
    - → Canagliflozin
    - → Empagliflozin
    - → Dapagliflozin

- DOC: ACE inhibitors - For CHF Overall
  - If stage worsens add β blockers
  - Still worsens add spironolactone
  - If patient recovers change to sacubitril

- **ACE inhibitors**
  - Contraindicated in black race
  - Alternative: Hydralazine + ISDN

Sacubitril

00:18:20

- **Neprilysin inhibitor**
  - Neprilysin enzyme:
    - → Neutral endopeptidase enzyme
    - → Present in liver
    - → Degrades natriuretic peptides
  - Increase the levels of natriuretic peptides - good for the heart
    - → They increase Na^+ loss in the urine (diuretic action)
    - → Decreases preload and afterload
- Also degrades angiotensin
  - Increase angiotensin levels
  - Bad for heart
  - Increases preload and afterload
- Hence given as: Sacubitril + Valsartan (angiotensin receptor inhibitor)
  - Combination is called ARNI
  - Neprilysin inhibitor + Angiotensin receptor inhibitor

ACE Inhibitors

00:22:00

- **Drugs**
  - Enalapril
  - Lisinopril

β Blockers

00:22:35

PYQ: FMGE 2023

- Theoretically, β blockers decreases CO
- At low dose (1/8th) - Do not reduce CO but reduce cardiac remodeling
- Maximum cardio protective drug
- Decrease mortality by 31%
- Only 4 drugs shows cardiac remodeling
  - Nebivolol
  - Bisoprolol
  - Metoprolol succinate
  - Carvedilol
  - Mnemonic: NBMC

Important Information

Verapamil and Diltiazem

- Calcium Channels Blocker Non-DHP type
- Absolutely contraindicated in CHF
- Reduce cardiac output
- No cardioprotective action
- Increase mortality in CHF

02. Symptoms Relief in HF

00:26:46

PYQ: INICET 2022

- **Artery dilator**
  - Reduce afterload
  - Treatment of hypertension in CHF
  - **Drugs**
    - → **CCBs:** DHP
      - Amlodipine
      - Nifedipine
    - → α blockers like prazosin

- **Veins dilator**
  - Reduce Preload
  - Treatment of
    - → Pulmonary edema (LVF)
    - → Pedal edema (RVF)
  - Drugs
    - → DOC: Loop diuretics > Thiazides
    - → Nitrates

Important Information

- Mannitol (diuretic) absolutely contraindicated in CHF
  - Because it increases preload

- **Combined dilators**
  - Dual effect
  - **Drugs**
    - → Nitroprusside
    - → Natriuretic peptide

Natriuretic Peptides

00:30:00

MOA

- **Natriuresis**
  - Sodium excretion in urine
  - Has diuretic effect
  - Causes vasodilation
  - Hence reduce preload and afterload

Physiology of Natriuretic Peptides

Endogenously produced for protection of heart
↓
High preload
↓
More blood supply to heart
↓
Leads to right atrial stretch
↓
Increase in central venous pressure
↓
Releases natriuretic peptides
↓
Reduces blood supply to heart

- **Atrial natriuretic peptide (ANP):** Synthesized by atrial muscles
- **Brain natriuretic peptide (BNP):** Synthesized by ventricles
- **C type of natriuretic peptides:** Synthesized by endothelial cells
- **Urodilatin:** Synthesized by kidneys

Synthetic Natriuretic Peptides

00:33:30

- Recombinant BNP
- Drug: Nesiritide
  - IV drug
  - Given for symptomatic relief in CHF
  - Side effect: Hypotension
- New drugs
  - Recombinant ANP - Carperitide (available in Japan)
  - Recombinant urodilatin: Ularitide (available in Japan)

Important Information

- Natriuretic peptides are degraded by neprilysin enzyme or NEP
- Sacubitril: NEP inhibitor - approved drug for CHF
- Racecadrotril and Ecadrotil: NEP inhibitor - under trial
- Omapatrilat and Sampatrilat: Dual NEP and ACE inhibitor - under trial

03. Inotropic Drugs

00:37:30

- Increase cardiac output
- Treatment of Decompensated HF

Myocardium

↓

Stimulation of β 1 receptor

↓

Activates adenylyl cyclase enzyme

↓

Increases cAMP

↓

Causes calcium influx

↓

Binds to troponin C

↓

Increase myosin and actin binding

↓

Increase in force of heart contraction

↓

Inotropic effect

- Phosphodiesterase 3 enzyme degrades cAMP

Drugs 00:39:43

1. β 1 agonists
2. Phosphodiesterase 3 Inhibitors (inodilators)
3. Levosimendan
   → PDE3 inhibitor
   → Calcium sensitizer: Increases calcium binding to troponin C
   → Potassium channel opener (vasodilator effect)
4. **Omecamtiv -** Directly activates myosin and actin
5. **Digoxin/ Digitalis**
   → Inhibits Na^+ K^+ ATPase
   → Only oral inotrope
   → Given in chronic decompensated HF

- 1st 4 drugs are IV - Given in acute decompensated HF

β 1 Agonists 00:43:08

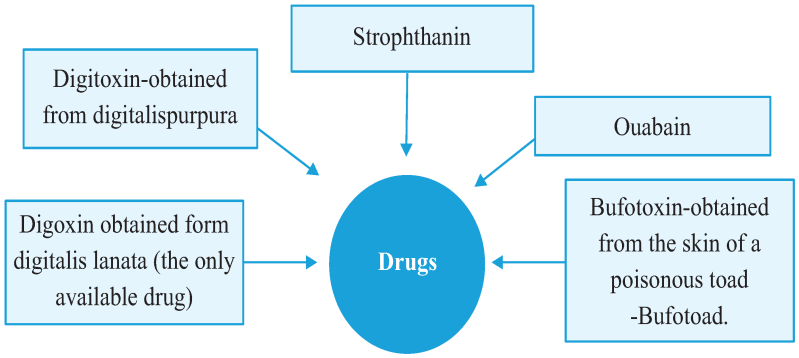
- **Dobutamine:** Specific β 1 agonists - DOC in acute decompensated HF
- **Norepinephrine**
  - Acts on α and β 1 receptor
  - DOC for acute decompensated HF with hypotension (cardiogenic shock)

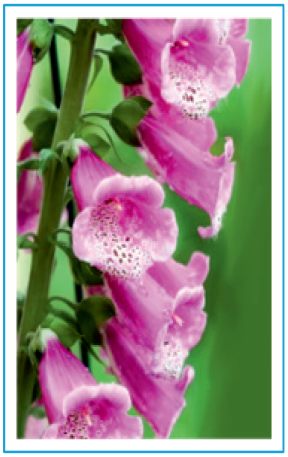
Inodilators 00:45:05

- Phosphodiesterase 3 inhibitors
- Increase cAMP levels in heart
- Increases force of contraction
- On blood vessels it produces vasodilation

- **Drugs**
  - Milrinone
  - Inamrinone (amrinone)
  - Outside India
    - → Enoximone
    - → Vesnarinone
- Given in acute decompensated HF resistant to β agonists
- More effective than β agonists
- DOC for acute decompensated HF due to β blocker overdose
- **Side effect:** Thrombocytopenia (increase bleeding)
  - Due to inhibition of PDE 3 enzyme in platelets

35 CARDIAC GLYCOSIDES DIGITAILS





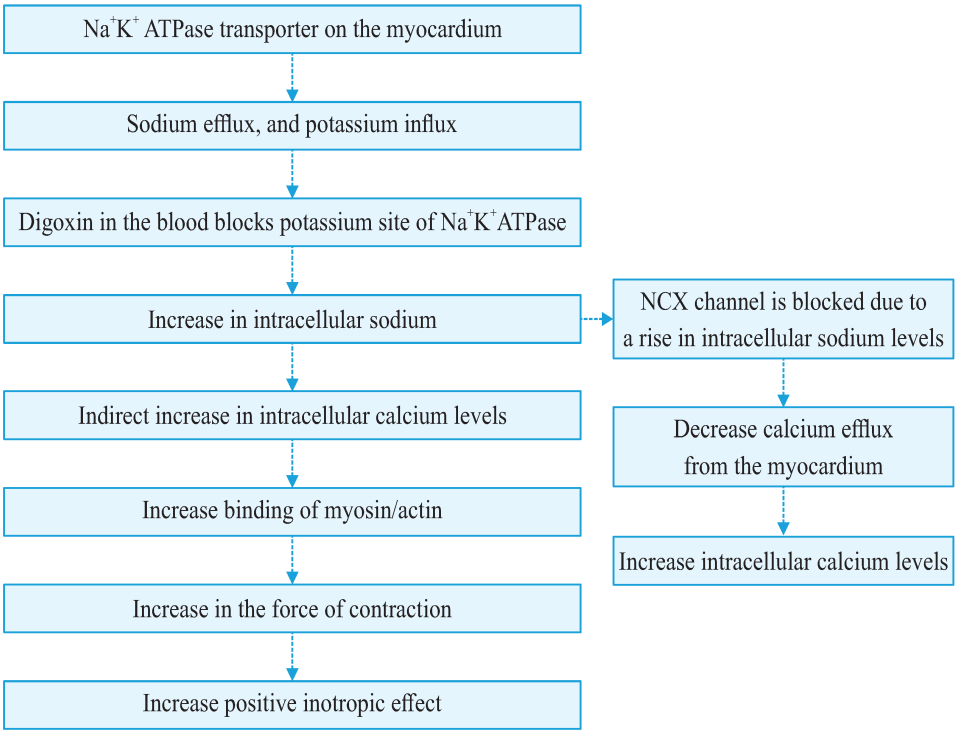
- Digitalis plant or foxglove plant - Flower;
  - Color - Purple to pink
  - Shape - Trumpet-like.

Digoxin

00:02:38

Mechanism of Action

MOA-1	Acts on the myocardium →	Inhibits Na^+K^+ ATPase on the muscles of the heart →	Positive inotropic drug →	Increases force of contraction →	Increases cardiac output
MOA-2	Inhibits • SA node →Negative chronotropic (reduces HR) • AV node → Negative dromotropic (reduced AV node conduction)	Digoxin stimulates vagus nerve	Inhibits SA and AV node	Vagomimetic effect of digoxin	

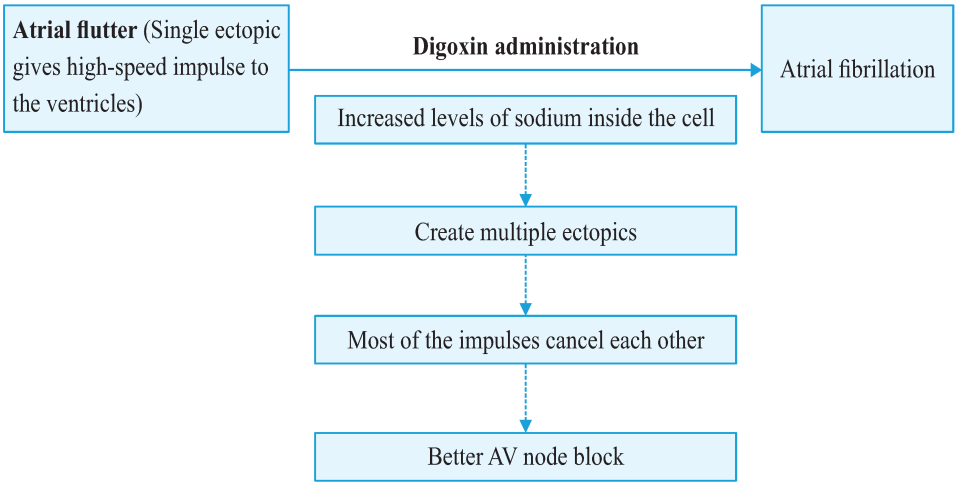


- Digoxin blocks the potassium site of Na^+K^+ATPase
  - Hyperkalemia → Decreases the effect of binding of Digoxin
  - Hypokalemia → Increased toxicity of digoxin → Increased binding of Digoxin leads to arrhythmias.
- Digoxin is contraindicated in hypokalemia (K^+ <3.5 meg/l).
- **Digoxin overdose** → Hyperkalemia in blood.

Uses

00:11:35

- **DOC:** Chronic heart failure
  - Positive inotropic drug → ↑ Cardiac output
- **Used in the treatment of** Atrial flutter and atrial fibrillation (SVT)
  - Aim - To prevent VT/VF by blocking AV nodes → Dromotropic effect.



Absorption

- Route of administration
  - Oral-CHF → Digoxin is the only drug
- IV-AHF

Distribution

- Vd-High Vd: 450 liters → Deposits in myocardium → Hemodialysis in digoxin toxicity is not effective as the drug is not present in the blood.
- T ½ : 40 hours → loading dose required for immediate effect
- Onset of action: It takes 5-8 days to show the effect of digoxin.

Pharmacokinetics of Digoxin

Metabolism:

- Not metabolized in the liver
- Safe to use in liver disease

Elimination:

- Unchanged in urine (kidney) by P-glycoprotein transporter
- Contraindicated in renal diseases

Therapeutic Index

- Digoxin is a narrow therapeutic index drug (Low safety margin) → Requires TDM.
- **Therapeutic range:** 0.5-2.0 ng/ml. PYQ: FMGE 2022

Important Information

Digitoxin is excreted in bile and it is safe for renal disease.

Digoxin Toxicity

- No role of hemodialysis due to large Vd.
- Antidote: Digibind or Digifab (FAB MAb against digoxin)
  - The FAB fragment binds to Digitoxin.
- Digibind is an Orphan drug (Rare indication)
- If Digibind is unavailable, Potassium chloride is used to treat Digoxin toxicity.
  - More potassium in the blood competes against digoxin and reduces digoxin toxicity.

00:24:20

Side effects

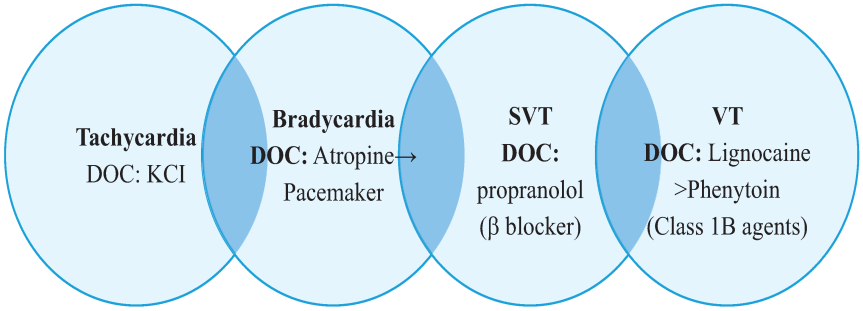
Non-cardiac side effects

- Most common: Nausea and vomiting due to GI irritation.
- Gynaecomastia: Displace testosterone from its receptor.
- Hyperkalemia
- Characteristics and specific visual abnormality: Yellow vision or Xanthopsia - Digoxin affects the Na^+K^+ channels on the retina.

Cardiac side effects

- Most common: Ventricular premature beats (Bigeminy)
- **Fatal:** VF/VT
- Aggressive treatment: Class IB antiarrhythmic - Lignocaine > Phenytoin.
- **Characteristic:** Atrial fibrillation (Non-PSVT) + AV node block.
- **Never causes** Atrial flutter.

Digoxin Induced Arrhythmias

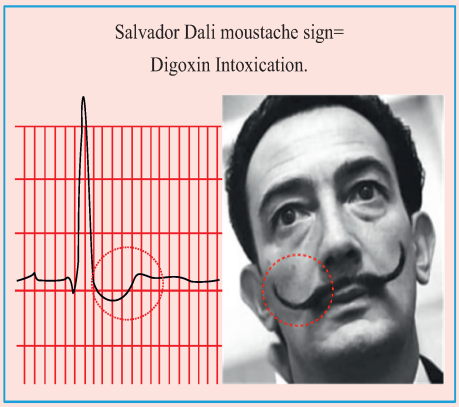


ECG Changes with Digoxin

Medicine

00:31:05

- ↑PR Interval → AV node block
- ↑RR Interval → SA node block
- Narrow QRS → Tells about Ven.depol - ↑ intracellular sodium.
- Inverted T wave → ↓ intracellular potassium.
- Reverse tick sign - Characteristic of digoxin toxicity.
  - Also known as Salvador Dali sign → Digoxin intoxication.



Drug Interaction of Digoxin

00:34:35

Loop and thiazide

- Increase Digoxin toxicity
- Reason: Hypokalemia

P-gp inhibitors

- Increase Digoxin toxicity
- Reason: Increase plasma digoxin (Not excreted via urine)
- Drugs
  - Verapamil
  - Amiodarone
  - Clarithromycin/Erythromycin
  - Ketoconazole

Cholesty-ramine and antacids

Reduce digoxin absorption from GIT, as it required bile for absorption

P-gp induces

- Reduces the effect of digoxin by increasing excretion of digoxin in urine.
- Drug-Rifampicin

Contraindications of Digoxin

00:37:05

- **Note- Mnemonic: HEART Will Cry**

High-output heart failure
HOCM
Electrolyte imbalances

- Hypokalaemia (<3.5 mcg/dl)→Causes arrhythmias due to binding of digoxin to the heart muscle.
- Hypercalcemia
- Hypomagnesemia→ Leads to hypercalcemia

AV node block
Renal failure
Thyroid abnormalities

Hyperthyroidism, which may lead to arrhythmias

WPW syndrome
Cardioversion

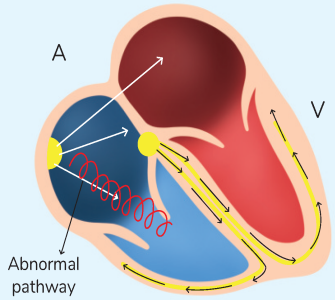
Wolff Parkinson White Syndrome

Medicine

00:40:00

Pathophysiology

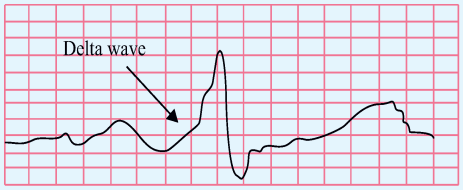
- Abnormal conductive pathway present between atria and ventricle.
- The patient suddenly goes into VF
- Bundle of kent-Abnormal conductive pathway
  - Early excitation of the ventricle Pre-excitable ventricles.



Normal electrical pathways

ECG

- Preexcitation wave or delta wave-Characteristic of WPW syndrome



Role of digoxin

Digoxin blocks the normal conductive pathway (AVnode) and increases conduction from the abnormal pathway.

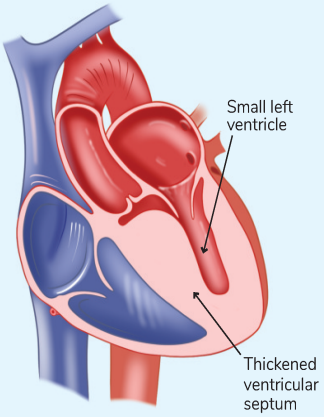
Treatment

- 1st: Radiofrequency ablation of abnormal pathways.
- If the patient is not eligible for surgery, then drugs are given.
  - No structural heart disease DOC: Flecainide
  - Structural heart disease- DOC:Procainamide

HOCM 00:44:40

Pathophysiology

- Hypertrophic obstructive cardiomyopathy
- Intraventricular septum-Hypertrophied and obstructs the aortic pathway
- If contractility increases, increased obstruction of the aortic outlet.



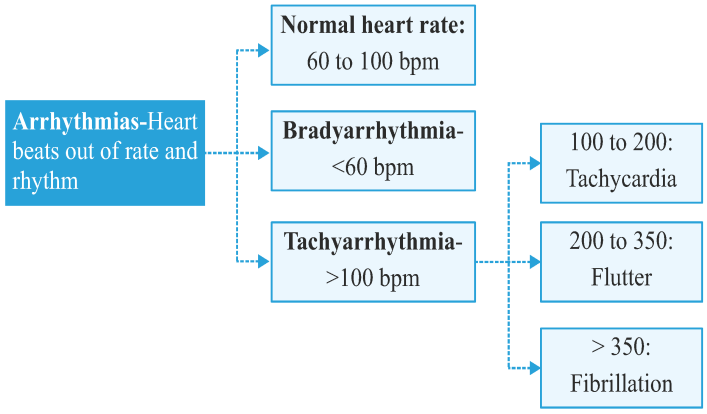
Treatment

- Reduce the contractility of the heart
- DOC: Beta-blockers, like atenolol and metoprolol.
- If asthma is present, DOC: CCB (Verapamil/Diltiazem)
- New drug-Mavacamten-Myosin inhibitor.
- Inhibit actin and myosin binding reduces contractility of the heart.

Overall DOC: Beta-blockers

Reduces the contractility and also reduces hypertrophy of the heart.

36 ARRHYTHMIAS

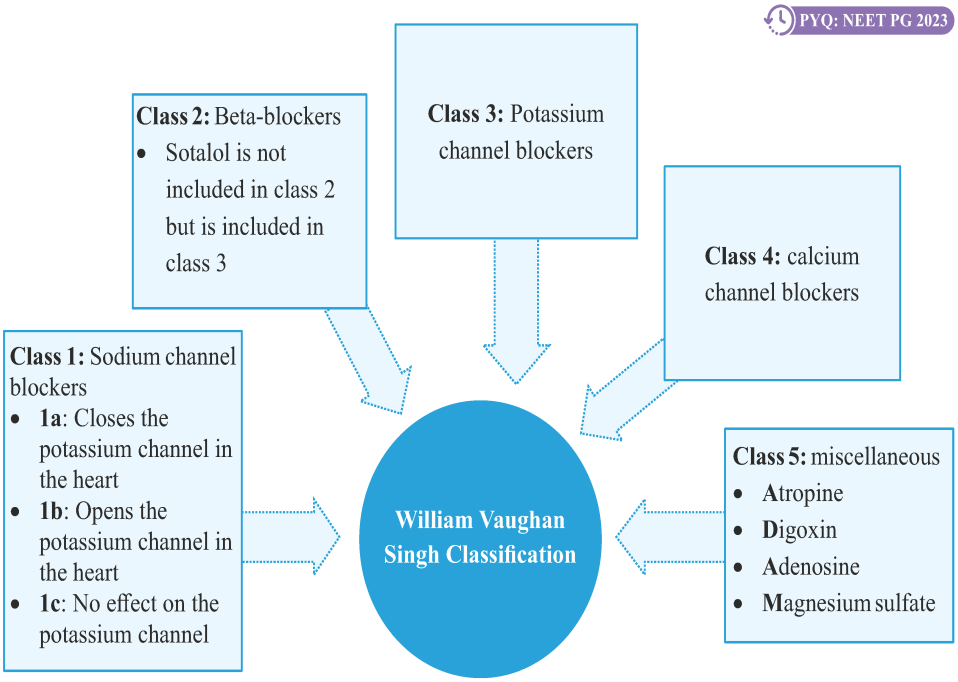


- **Flutter and fibrillation -** Always pathological
  - Ineffective contraction occurs
  - Leading to a decrease in cardiac output

Antiarrhythmic Drugs

00:02:20

PYQ: NEET PG 2023



Bradyarrhythmias

00:05:30

Causes

- Defect in impulse generation (defect in SA node) – called sick sinus syndrome
  - Increase in RR interval
  - Next heartbeat is delayed
- Defect in impulse propagation
  - AV node block or bundle branch block
  - Increase in PR interval

Treatment

- DOC of all bradyarrhythmias: Atropine
- Definitive treatment: Cardiac Pacemaker

Tachyarrhythmias

Medicine

00:08:48

2 Conducting fibers in the heart

Slow conducting fibers

- SA node and AV node
- Lack sodium channels

Fast conducting fibers

- Muscles of the heart, Atrial muscles Ventricular muscles
- Contains sodium channels

Slow Conducting Fibers

00:10:25

Slow conducting fibers

↓

Lack Sodium channels

↓

But contains calcium and potassium channels

↓

When an action potential is generated at the SA and AV node

↓

At the resting phase - SA and AV

↓

At depolarization – Calcium ions move inside (calcium influx)

↓

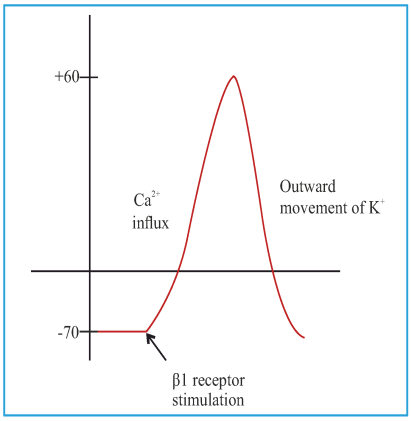
Increases positive charge is SA and AV node

↓

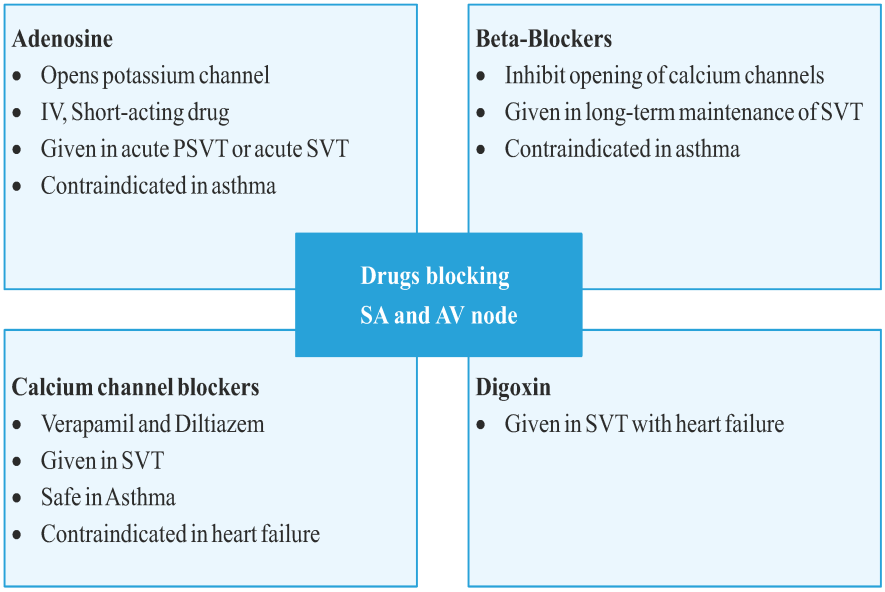
Excitation of SA and AV node

↓

Repolarization is achieved by the movement of potassium outside the cell

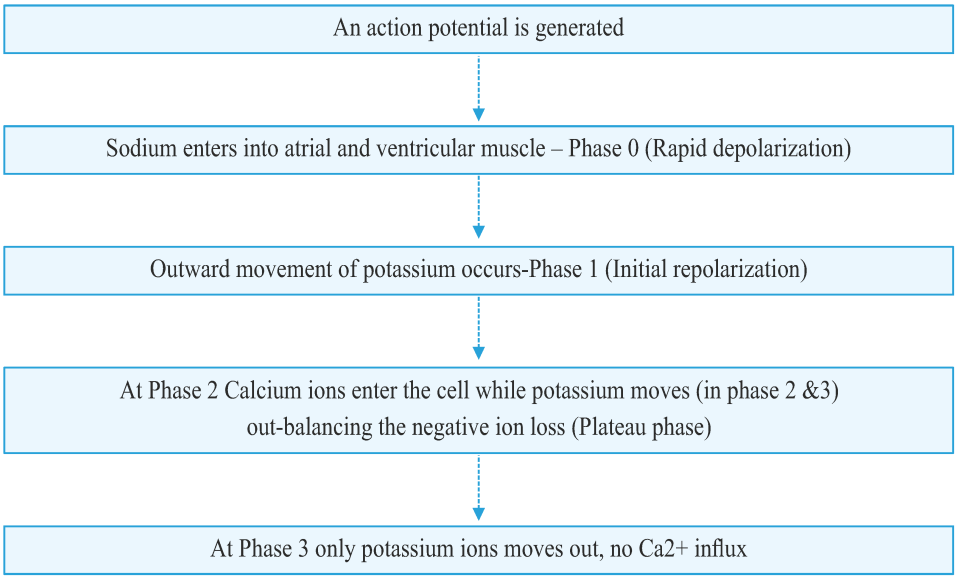


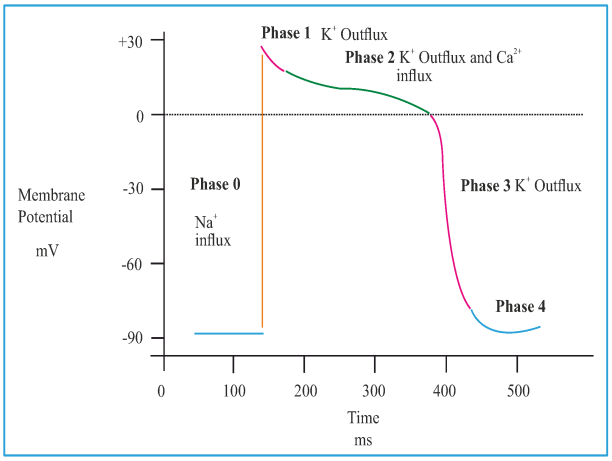
- SA and AV node blockers are used in SVT (Atrial flutter and fibrillation)
  - If the impulse goes to the ventricle through the AV node - Leads to ventricular tachycardia
  - The main motive is to prevent Ventricular tachycardia



Fast Conducting Fibers 00:19:25

- Contains sodium channels
- Also, contain
  - Calcium channels
  - Potassium channels





PYQ: NEET PG 2020, 2023

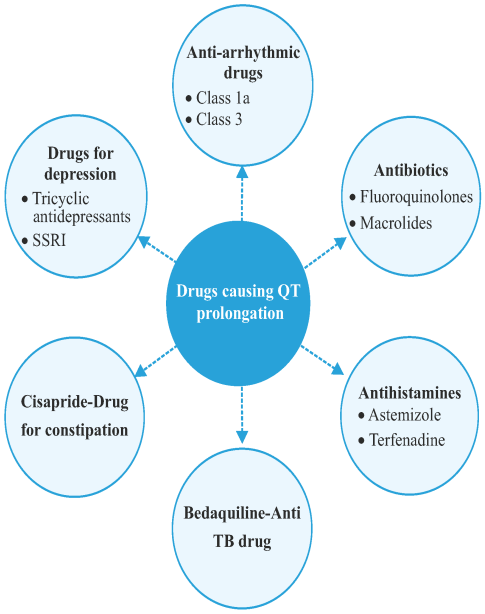
PYQ: FMGE 2021

Sodium channel blockers	Potassium channel blocker

• Affects phase 0 – Reduces the slope (dv/dt)
• Inhibits depolarization of atria and ventricle
• DOC in ventricular tachycardia
  ○ Amiodarone (1st choice)
  ○ Lignocaine
  ○ Sotalol
  ○ Procainamide
	• Delays phase 1, 2 and 3
	• Inhibits repolarization of the heart
	• Action potential duration is increased
	• T wave signifies ventricular repolarization
	• This leads to prolonged QT interval on ECG

Relative refractory period

- Prolongation of the QT interval leads to the formation of the relative refractory period
  - Sodium channels will be recovered
  - If any impulse is generated it leads to depolarization before complete repolarization
- This causes a condition called Torsades de pointes
  - DOC: Magnesium sulfate
    → Blocks calcium channels reducing action potential duration and preventing depolarization



Class 1 Antiarrhythmic Drugs

- Sodium channel blockers
  - 3 types

	1a	1b	1c
Na^+ channel	Intermediate block in an open state	Rapid block in an inactivated state	Slowest block in both state
Duration	1-10 msec(Open state)	<1 msec (Closed/inactive state)	>10 msec (Both)
K^+ channel	Close	Open	No action
Action potential	• Phase 0 is reduced • Increase action potential duration	• Phase 0 is reduced • Decrease action potential duration	• Phase 0 is reduced • No effect on action potential duration
Use	Ventricular and atrial tachycardia	Only ventricular tachycardia	Resistant cases of Ventricular and atrial tachycardia
Drugs	• Quinidine • Procainamide • Disopyramide	• Lignocaine • Phenytoin • Mexiletine • Tocainide	• Encainide • Flecainide • Propafenone • Moricizine

Class 1a Antiarrhytmics

00:40:24

Quinidine

Facts

- 1st antiarrhythmic drug to be made
- D-isomer of Quinine (1st antimalarial drug)
- Obtained from bark of cinchona

Action

- Has additional atropine like property
  - Increased AV node conduction
  - Main side effect – Tachycardia
- Metabolized by CYP2D6

Side effects

- Diarrhea (most common)
- Hypotension (due to blockage of alpha receptors on blood vessles)
- Hypoglycemia (due to increase in insulin secretion)
- Cinchonism (neurotoxicity)
  - Tinnitus
  - Deafness
  - Vertigo

Precaution

- Always given in 5% dextrose solution (to prevent hypoglycemia)

Procainamide

Action

- Has beta blocking action
  - Blocks AV node
  - Main side effect: Bradycardia

Uses

- Used in treatment of
  - Ventricular tachycardia
  - WPW syndrome

Pharmacokinetics

- Part of SHIP drug
  - Metabolized by acetylation
  - Main side effect: drug induced lupus erythematosus
  - May cause sulfa allergy – Leads to bone marrow suppression (agranulocytosis)

Disopyramide

Action

- Has atropine like properties
- Increased AV node conduction

Side effects

- Similar to atropine like effects
  - Dry eyes and mouth
  - Constipation
  - Urinary retention

Ajmaline

Facts

- New drug in class 1a
- Not used in arrhythmia treatment

Uses

- Used in diagnosis of Brugada syndrome
  - Genetic condition
  - Defective sodium channels – Open for long duration
  - Ajmaline can't block sodium channel in Brugada syndrome

Class 1b Antiarrhytmics

00:49:00

Lignocaine

Other Name

- Lidocaine, Xylocaine

Actions

- It is a local anesthetic
  - Contain various preservatives
  - Pure form of lignocaine is used in Arrythmia

Uses

- Used in the treatment of Ventricular tachycardia

Ventricle muscles → Contain sodium channels → Higher perfusion of ventricles → Blocking of sodium channels → Ventricular rate is reduced

Pharmacokinetics

- Only IV drug
  - Oral form-Degraded in the liver
  - Not absorbed
  - Has very high first pass metabolism in liver

Side effects

- Causes bradycardia
- Neurotoxicity

Neurotoxicity of lignocaine → Excitation of brain leads to nystagmus (excessive movement of eyes), seizures → Suppression of brain leads to respiratory depression

Antidote for toxicity of lignocaine

- 20% intralipid (antidote)

Phenytoin

- Anti epileptic drug
- MOA- Blocks Na^+ channels
- Treatment -ventricular tachycardia caused due to digoxin
  - DOC – Lignocaine

Mexiletine

- Oral prodrug of lignocaine
- Treatment – Maintenance of ventricular tachycardia
  - Approved for diabetic neuropathic pain (DOC-pregabalin)

Tocainide

- Used to treat arrhythmias

Class 1C agents Antiarrhytmics

00:55:55

- Given as a reserve drug in resistant diseases of ventricular tachycardia/atrial tachycardia
- Contraindication- MI/ Structural heart disease
  - CAST trial- Proven that class 1C drugs increase mortality in post-MI/Structural heart disease patients
- DOC for Structural heart disease- Amiodarone
  - Reduce mortality
- Flecainide is a drug approved for the treatment of WPW syndrome

Class 2 Antiarrhythmic Drugs

00:58:52

Class 2 Antiarrhythmic Drugs
All Beta blockers except Sotalol

Non Selective beta blockers

- Propranolol
- Timolol
- Nadolol

Cardioselective beta blockers

- Metoprolol
- Atenolol
- Esmolol- Short acting beta blockers
  - Hence, IV β blocker recommended for intraoperative tachycardia

Drug of choice

- Sympathetic tachycardia
  - Occurs in Fear, Fever, Hyperthyroidism, Pheochromocytoma
- Long term maintenance in supraventricular tachycardia

Side effects

- Bradycardia, AV nodal block

Antidote

- Antidote for beta blocker toxicity – Glucagon hormone

Beta blockers toxicity → Glucagon hormone → Glucagon hormone receptors are present in SA and AV nodes → Stimulation of SA & AV nodes → Increase in heart rate

Class 3 Antiarrhythmic Drugs

01:02:58

- **MOA**
  - Potassium channel blockers
  - Increase the duration of action potential
  - Increases the risk of QT prolongation
  - Increases torsades de pointes
- **Uses**
  - Flutter and fibrillation
- **Drugs**

Bretylium	Medical defibrillator
Dofetilide (Oral) **Ibutilide (IV)**	• Pure potassium channel blockers ○ Increases action potential duration • Treat atrial flutter and fibrillation

Vernakalant
Amiodarone/Dronedarone
Sotalol
	• Other Name- Multi ion channel blockers
	  ○ Blocks Na^+, K^+, Ca^{2+}, beta blocking action
	  → Blocks Na^+: Decrease phase 0 slope
	  → Blocks K^+: Increase duration of action potential
	• Treat both atrial and ventricular fibrillation

Sotalol

- Beta blockers + Class 3 Agent (Blocks K+ channels)
  - Unsafe or contraindicated in renal failure
- Non selective beta blocker

Important Information

- Shortest acting antiarrhythmic drug is Adenosine with the half life of 9 secs

Amiodarone 01:08:27

Drug of choice

- All types of atrial and ventricular fibrillation
- Ventricular fibrillation after myocardial infarction
- Most effective and reduces mortality
- Recommended in all types of arrhythmias except long QT syndrome or torsades de pointes

Pharmacokinetics

- Longest acting anti arrhythmic drug
- Half life-close to 60 days
- Requires loading dose
- Metabolism -CYP3A4 enzyme

MOA

- Inhibitor of CYP3A4

Adverse effects

- Amiodarone contains iodine (37%)
- I2 causing hypothyroidism - Wolf Chaikoff effect

Excessive of iodine → Decrease the synthesis and release of T3 and T4 → Periphery – inhibit the conversion of T4 to T3 → Hypothyroidism

- I2 causing hyperthyroidism -Jod basedow effect

Hyperthyroidism → Increases the synthesis of T3/T4

- Photosensitivity skin
  - Skin color: purple, violet
  - Other name- purple man syndrome, smurf syndrome
- Peripheral neuropathy
- Pulmonary fibrosis
  - Hypoxia – Interstitial lung disease
- Chronic liver disease /Cirrhosis of liver

Ocular Side effects

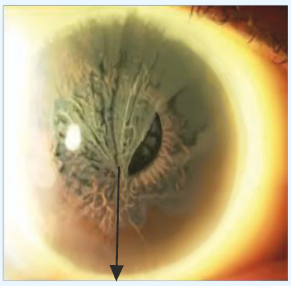
- Deposits in cornea, retina, lens

Cornea Verticillata	Other name-Vortex keratopathy Reversible micro disposition of amiodarone
Anterior subcapsular cataract	Deposition of amiodarone in lens
Retinal micro deposition	Deposition of amiodarone in retina

Dronedarone

- Modification of amidarone
- Doesn't contain iodine

Drug-induced vortex keratopathy



Drug-induced vortex keratopathy
- White hassle lights in the shape of tree
- Amiodarone causes vortex keratopathy
- Cornea: Chloroquine, Chlorpromazine (Antipsychotic)
- Gets: Gold, Gentamicin
- Inked: Indomethacin

Purple man syndrome
- Side effect of amiodarone
- Purple toe syndrome- Side effect of Warfarin
- Purple glove syndrome- Side effect of phenytoin

Class 4 Antiarrhythmic Drugs

01:20:05

PYQ: INICET 2022

Calcium channel blockers

- Verapamil
- Diltiazem

Uses

- Treat SVT and Prevent VT
- Blocks AV node

Contraindication

- Ventricular tachycardia
- Never combined with beta blockers as it causes bradycardia (Ultimately leads to reduced cardiac output)

Toxicity

- IV calcium gluconate (Antidote)

Antidote

Drugs	Antidote
Lignocaine	20% intralipid
Amiodarone	
Verapamil	IV Calcium gluconate
Diltiazem	
Beta blockers	Glucagon hormone

Class 5 Antiarrhythmic Drugs

01:23:04

- **Note: Mnemonic: ADAM**

A–Atropine
- DOC-Bradyarrhythmias

D- Digoxin
- Treat supra ventricular tachycardia in heart failure patients
- Treat atrial flutter/fibrillation

Miscellaneous Drugs

A- Adenosine
- **DOC-** Acute attack of paroxysmal supraventricular tachycardia

M-Magnesium sulfate
- DOC – Torsades de pointes

Adenosine

Mechanism of action

Adenosine → Acts on adenosine A1 receptor (Gi type of GPCR) located in SA and AV node → Open potassium channels → Block SA/AV node

Pharmacokinetics

- IV drug
- Shortest acting antiarrhythmic drug
- Degraded by adenosine deaminase enzyme
- T ½ : 9 seconds
- DOC for the acute attack of PSVT or SVT

ROA

- Given in a proximal vein (central line)
- Fast injection-Rapid bolus and flush with saline

Dose

- 1st injection-6mg
- 2nd injection-12mg
- 3rd injection -12 mg
- Maximum 3 injections of adenosine
- Maximum dose: 30 mg

Side effects

- Asthma-caused by bronchoconstriction by acting on adenosine A1 receptor in bronchus
- Vasodilation-manifesting as flushing and hypotension

Important Information

- Theophylline, Caffeine are Bronchodilator and block adenosine A1 receptor

Management of Arrhythmias

Medicine 01:30:58

Hemodynamically Unstable	DC shock/ Cardioversion
Hemodynamically Stable	Anti arrhythmic drugs

Atrial Tachyarrhythmia

Other Name	Supraventricular tachycardia (SVT)
Goal	Prevent ventricular tachycardia
Drugs-AV nodal blockers	• Adenosine-Acute attack of SVT • Beta blockers-Long term maintenance of SVT • Calcium channel blockers-Asthma • Digoxin-Heart failure

Suppression of atrial muscles-reduce atrial rate	• Na^+ channel blockers
	• DOC – Amiodarone
	• Other drugs
	  ○ Ibutilide
	  ○ Dofetilide

Anticoagulants-decreases the clotting factors	• DOC- Warfarin • Others – Injections of heparin

PSVT- Paroxysmal Supraventricular Tachycardia

01:34:32

Pathophysiology

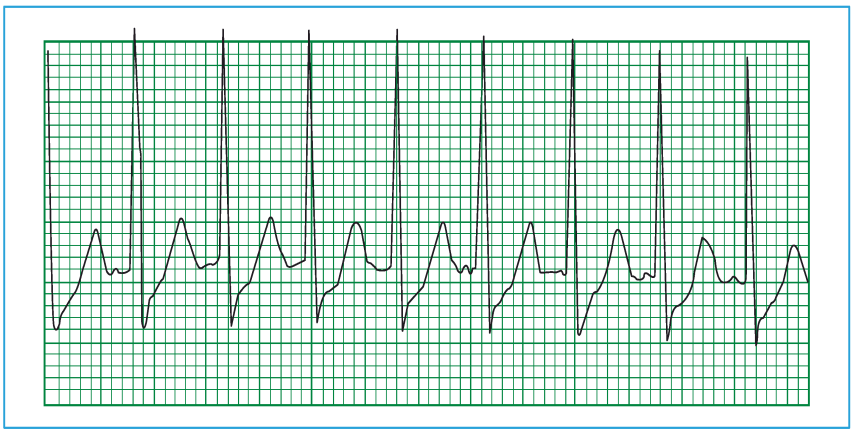
Fibers of AV node become abnormal → Abnormal conduction of impulses → Stimulation of both atrial and ventricles at the same time

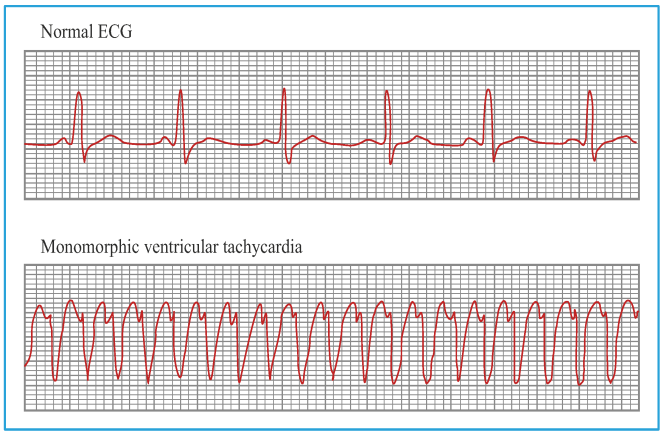
ECG-Ventricular waves

- QRS complex
- T waves
- Absence of P Wave
- Heart rate-Very high

Treatment -Block AV node

- Vagal stimulation -Vagal maneuvers through valsalva, oculocardiac reflex (if not treated)
  - Ice pack over eyes
  - Eye massage
- IV adenosine in 3 injections
  - 6 mg →12mg →12mg as rapid push
  - Recommended in acute attack of PSVT
- Maintenance -beta blockers
  - Recommended in chronic attack of PSVT
- Contraindications in asthma: Beta-blockers, adenosine
- Asthma-Recommend calcium channel blockers
  - Verapamil
  - Diltiazem





- Monographic ventricular tachycardia- Ventricle is bearing more
- DOC- Aminodarone
  - VT after MI
- VT after digoxin- DOC is Lignocaine

Long QT Syndrome

01:39:14

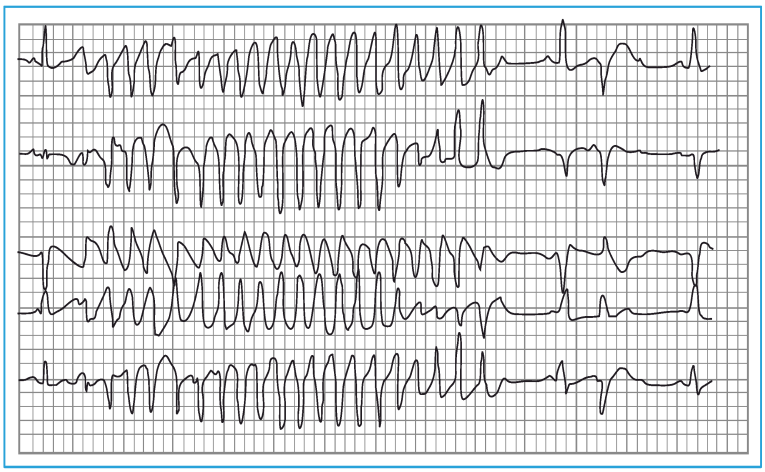
Types

Congenital long QT Syndrome

DOC- Beta blockers

Acquired long QT Syndrome

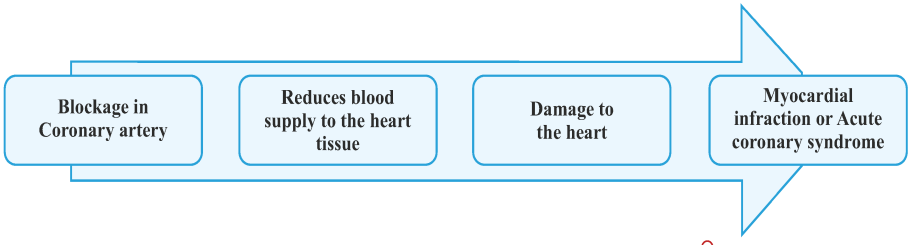
- Precipitated as an arrhythmia- Torsades de pointes
- Other Name- Polymorphic VT



Torsades de pointes

- Different shapes of QRS complex- Polymorphic VT
- DOC- Magnesium sulfate
  - Magnesium sulfate is not effective in treating congenital long QT Syndrome

37 MYOCARDIAL INFARCTION



Types of Acute Coronary Syndrome

Medicine

00:00:54

	Unstable Angina	NSTEMI- Non-ST Elevation MI	STEMI- ST Elevation MI
Coronary artery blockage leads to	Ischemia	Partial thickness infarct	Full thickness or transmural infarct
ECG	ST Depression	ST Depression	ST Elevation
Cardiac biomarkers	Negative	Positive	Positive

Cause

00:04:14

Most common cause: Atherosclerosis – excessive deposition of fat and glucose (due to Diabetes mellitus, Dyslipidemia)

↓

Endothelial damage

↓

Platelets and fibrin block the blood vessels

↓

Decreased blood supply

↓

Myocardial infarction

↓

Complications

Management

00:05:50

Initial symptomatic treatment

MONAS

- **Morphine**
  - Reduce chest pain, anxiety, and apprehension
- **Oxygen**
  - Treat hypoxia
- **Nitroglycerin (NTG)**
  - Decreases Preload
- **Aspirin**
  - Antiplatelet effect
- **Statins**
  - Stabilize thrombus

Steps Followed in the Management

Medicine

Aspirin 325 mg (oral) + oxygen

↓

NTG 0.5 mg S/L (Max 3 times)

↓

Morphine 2-4 mg IV

↓

Atorvastatin 80 mg or Rosuvastatin 40 mg

Other antiplatelets added along with aspirin are:

- DAPT - Dual Antiplatelet Therapy
  - Clopidogrel
  - Prasugrel
  - Ticagrelor/Cangrelor

Prevent and Treat Complications

00:10:10

Prevention

- **Beta – blockers given in acute attack → Atenolol, Metoprolol**
  - Prevent infarct expansion
  - Prevent arrhythmias due to sudden sympathetic discharge
- **ACE inhibitors – Ramipril, Perindopril, etc**
  - Prevent infarct expansion

Already occurred complications

- **Hypovolemia/Metabolic acidosis**
  - IV fluids with sodium bicarbonate

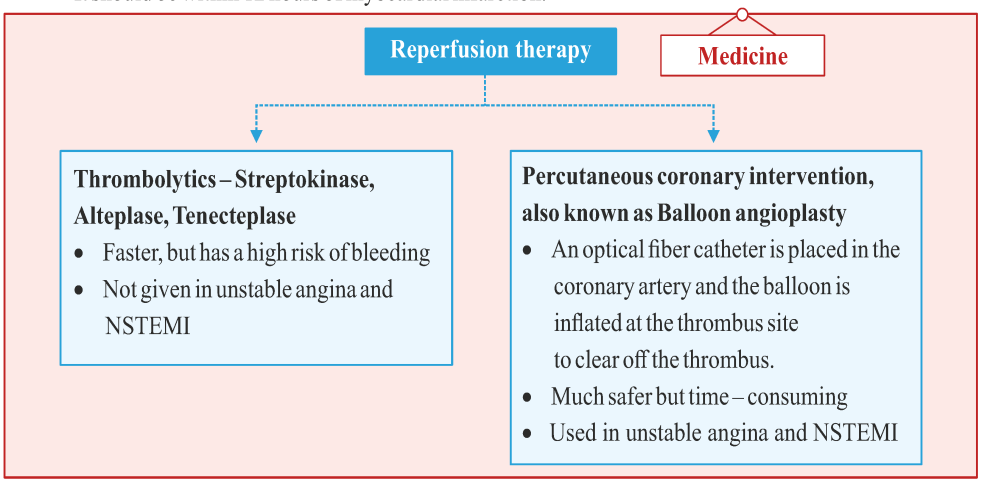
PYQ: NEET PG 2022

- **Cardiac arrest**
  - DC shock/cardioversion in case of asystole →inj. Epinephrine 1:10000 IV.
  - In case of ventricular fibrillation, DOC: Amiodarone

PYQ: NEET PG 2023

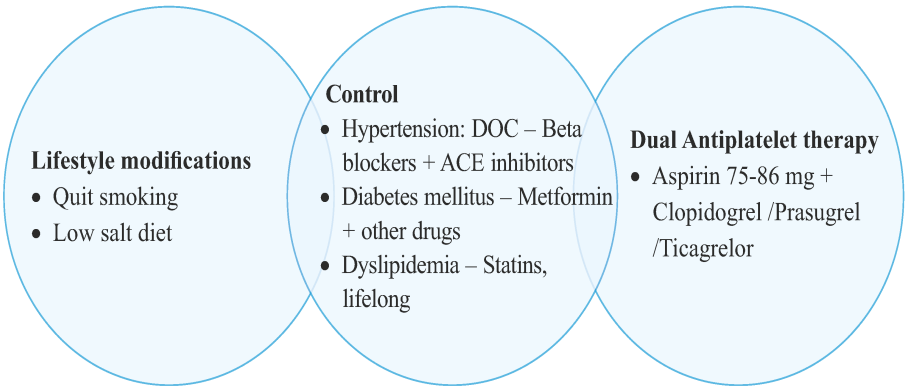
Definitive Treatment: Reperfusion Therapy 00:13:40

- Reperfusion therapy: Opening of coronary artery.
- It should be within 12 hours of myocardial infarction.



- In STEMI- First thrombolytics are given and later a definitive PCI is planned.
- **Time to start**
  - Thrombolytics - Door-to-needle time → <30 mins
  - PCI - Door to balloon time → <90 mins

Secondary Prophylaxis 00:20:45

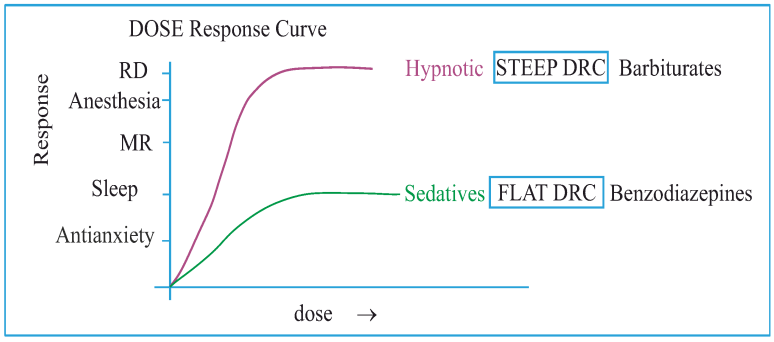


38 SEDATIVE HYPNOTICS DRUGS FOR INSOMNIA

- Sedatives: Induce calmness, remove anxiety
- Hypnotics: Induce sleep
- Sedatives in higher dose: Hypnotic

Sedatives
↓
Higher dose
↓
Hypnotics
↓
Further increase in dose
↓
Muscle relaxation
↓
Higher dose
↓
Unconsciousness and loss of sensation (Anesthesia)
↓
Respiratory depression/Coma (Higher dose)
↓
Death due to overdose of sedatives and hypnotics

Dose Response Curve



- X-axis: Dose
- Y-axis: Response
- Low response: Antianxiety effect
- Lastly: Respiratory depression
- Hypnotics: Steep DRC
  - Produce sudden respiratory depression
  - Barbiturates
- Sedatives: Flat DRC
  - Benzodiazepines

Drugs in Sedative and Hypnotics

00:03:35

1. Barbiturates
2. Benzodiazepines

3. Atypical benzodiazepines (Z drugs)
4. Melatonin and new drugs
5. Alcohols

Barbiturates and Benzodiazepines

Psychiatry

- Benzodiazepines and barbiturates: Activation of GABA-A chloride channels
  - Other Name: GABA-A chloride channel agonists

GABA receptor

- Inhibitory neurotransmitter
- It is of three types

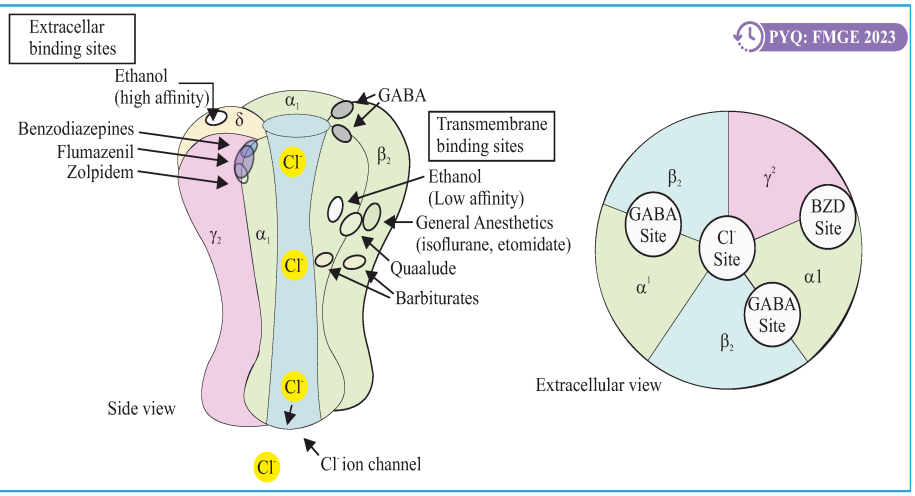
GABA-A	• Ionotropic receptor
	• It is a chloride channel
	  ○ Hyperpolarization of the neurons
	• Drugs
	  ○ Benzodiazepines
	  ○ Barbiturates

GABA-B	• G protein coupled receptor • Gi type of GPCR ○ Potassium efflux • Drug: Baclofen
GABA-C	• Ionotropic receptor • Has chloride channels ○ Hyperpolarization of the neurons • Location: Retina

GABA-A Chloride Channel

- Ionotropic receptors
- Shape: Flower like with five subunits
  - Pentameric rosette type
    - → 2 α
    - → 2 β
    - → 1 γ
- Has five subunits with a central pore

PYQ: FMGE 2023



GABA

↓

Attaches on α and β junction

↓

Opening of the chloride pore

↓

Chloride moves inside the neuron

Action of Barbiturates on GABA-A

- Has no specific site - Binds to multiple sites
- Low dose: GABA facilitatory
- High dose: GABA mimetics - Open the channels directly
- Higher dose: Non specific
  - Blocks Na^{+}, Ca^{2+}, and glutamate (Excitatory neurotransmitter)
- Very dangerous drugs
- Pharmacokinetics
  - **Mnemonic:** NEHA
  - Has narrow therapeutic index
    → Low safety margin
    → Require therapeutic drug monitoring (TDM)
  - Enzyme inducers
    → CYP + glucuronide
    → Has drug interactions
  - Highly addictive drugs
  - Antidote: No specific antidote

Action of Benzodiazepines on GABA-A

GABA

↓

Attaches on α and γ junction

↓

GABA facilitatory (increase the binding of endogenous GABA)

↓

Chloride moves inside the neuron

- Safe drugs: Do not require monitoring
- Not inducers: Less drug interactions
- Less addiction
- Specific antidote: Flumazenil

α-γ Junction	• Agonists: Benzodiazepines • Competitive antagonist: Flumazenil • Inverse agonist : β carboline ○ Side effects: Seizures
α-β Junction	• Agonist: GABA (Endogenous) ○ Muscimol (Exogenous) • Competitive antagonist: Bicucilline • Direct chloride pore blocker: Picrotoxin

Flumazenil 00:19:20

- Antidote for benzodiazepine poisoning
- Half life: 30-60 mins
- Dose: 5 mg repetitive IV injection

Important Information

- Any antidote is always given as repetitive IV injections
  - Opioid poisoning: Repetitive injection of naloxone
  - Organophosphate poisoning: Repetitive injection of atropine

1. Barbiturates 00:21:00

- Chemical nature: Urea + Malonic acid
- Divided into three types

Ultra short acting barbiturates	• Action is terminated by: Redistribution into fats ○ After leaving the brain (site of action), they get deposited in fats • Thiopentone: Sodium pentothal ○ ROA: IV ○ Induce general anesthesia ○ Action: 2-5 mins ○ Has cardioprotective, neuroprotective effect → Decreases the O_2 demand of heart and neurone ○ Has antithyroid effect ○ DOC: Truth-Serum → Other Name: Narcoanalysis → Sedative + decreases cognition – Other drug used - Hyoscine ○ 3As → Acidic drug mixed with sodium bicarbonate: Alkaline → Acute intermittent porphyria - Contraindication of all barbiturates → Arterial injection: Not recommended – Leads to thrombosis – Management: Do not take out the syringe and administer Streptokinase • Methohexitone ○ Reduces seizure threshold → Easily provoke seizures ○ DOC: Electroconvulsive therapy → Other drugs – Propofol – Etomidate – Ketamine + ECT: Preferred in depression – Fentanyl: Opioid
Short acting barbiturates	• It includes (Ends with -barbitone or -barbital) ○ Butobarbitone ○ Amobarbitone ○ Pentobarbitone ○ Secobarbital • ROA: IV in ICU patients preoperatively

Long acting barbiturates	• Drugs include ○ Phenobarbitone ○ Primidone: Active drug → Converted to phenobarbitone → Treat: Essential tremors – Propranolol, primidone

A. Phenobarbitone

- DOC:
  - Neonatal seizures
  - Neonatal jaundice: Crigler Najjar syndrome type 2
  - Gilbert syndrome
    - → Deficiency of UDP-GT enzyme
    - → Reason: Enzyme inducers

Glucuronide not attached to bilirubin
↓
Bilirubin will not become water soluble
↓
Levels of bilirubin is increased
↓
Formation of jaundice

- Safest drug in new born child

Pharmacokinetics

- Metabolism: CYP3A4 enzyme
  - Induce CYP3A4 activity
- Contraindication: Acute intermittent porphyria

Side effects

- Paradoxical excitation: Seen in children
- Hyperkinesia
- Induce seizures
- Excessive sensation
- Excessive pain perception

Acute intermittent porphyria

- Defective synthesis of heme
  - Accumulation of porphyrin
- Side effects
  - Pallor/Anemic
  - Craving for blood
  - Abdominal pain and vomiting
  - Photosensitivity
- Contraindication: Barbiturates

Barbiturates are CYP enzyme inducers
↓
CYP enzyme contains heme
↓
Increase in heme demand of the body
↓
More porphyrins get accumulated - hence barbiturates are contraindicated

Important Information

- Benzodiazepines: Safe in porphyria

Drugs contraindicated in porphyria

- **Mnemonic:** SEVERE POBA
  - Sulfonamides
  - Estrogen
  - Valproate
  - Ergotamine
  - Rifampicin
  - Erythromycin
  - Phenytoin
  - OCP
  - Barbiturates
  - Alcohol

Barbiturates Poisoning 00:41:26

- Clinical features
  - Unconscious
  - Hypotension
  - Bullous eruption on skin
  - Respiratory depression (death)
- Treatment: Forced alkaline diuresis by using Sodium bicarbonate
  - Last option: Hemodialysis
  - Earlier times: Respiratory stimulants

Respiratory stimulants

↓

Directly stimulate the respiratory centres in brain

→ Other Name of respiratory stimulants: Analeptic drug
- Bemegride
- Doxapram
- Picrotoxin

- Has no specific antidote

2. Benzodiazepines 00:44:28

- Acts on α-γ subunit of GABA-A chloride channels
  - GABA-A facilitatory

Antiseizure drugs	• **Mnemonic:** DLCCM ○ Diazepam: Febrile seizures ○ Lorazepam: Status epilepticus ○ Clonazepam ○ Clobazepam ○ Midazolam
Insomnia	• **Mnemonic:** FTEQT ○ Flurazepam ○ Temazepam ○ Estazolam ○ Quazepam ○ Triazolam

Pre anesthetic medication	• It helps in
	  ○ Sedation
	  ○ Anti-anxiety effect
	  ○ Produce anterograde amnesia
	
	• **Mnemonic:** DLMR
	  ○ Diazepam
	  ○ Lorazepam
	  ○ Midazolam
	  ○ Remimazolam

Anti-anxiety drugs	• **Mnemonic:** DCOLA
	  ○ Diazepam
	  ○ Clonazepam
	  ○ Oxazepam
	  ○ Lorazepam
	  ○ Alprazolam

Muscle relaxants	• Diazepam: Stimulate GABA-A receptor
	  ○ Addictive
	• Baclofen: Acts on GABA-B receptor
	  ○ Non benzodiazepines
	  ○ Non addictive and non sedative
	• Brain: GABA-A receptor
	• Spinal cord: GABA-B receptor

Anti-Anxiety

- Performance anxiety: Treated with propranolol (β blocker)
- Anxiety disorder
  - Common disorder: Generalised anxiety disorder
  - Suffers from panic attack
    → Acute attack of anxiety
    → DOC: Benzodiazepines
  - Maintenance of anxiety disorder: Selective serotonin reuptake inhibitors (DOC)

Barbiturates and benzodiazepine: Automatism 00:53:25

- Anterograde amnesia: Repetitive self medication
  - Leads to overdose or poisoning
- Automatism: Seen with alcohol
- Alcohol, opioids: Increase sedative effect of benzodiazepine, barbiturates

Metabolism of Benzodiazepines

Class A drugs

Benzodiazepines (Active drugs)
↓
CYP3A4 enzyme in liver
↓
Benzodiazepines are converted to another active form
↓
Excreted out in urine

- Example: Diazepam→ Oxazepam: Excreted in urine
- Includes all benzodiazepines except the 4 class B drugs

Class B drugs

Active drugs of benzodiazepines
↓
No CYP3A4 metabolism in liver
↓
Excreted in urine

- It includes drugs like
  - **Mnemonic:** LOTE-Safe in liver diseases
    → Lorazepam
    → Oxazepam
    → Temazepam
    → Estazolam
- Longest acting benzodiazepine: Flurazepam
- Shortest acting: Remimazolam > Midazolam
- Maximum plasma protein binding: Diazepam
- Least plasma protein binding: Flurazepam

Triazolam	• Side effect: Psychosis
Flurazepam	• Side effects: Nightmares
Alprazolam	• Mood elevating action ○ Antidepressant effect
Midazolam	• Recommended in many routes • IM injection controls status epilepticus • Intrathecal: Pain relief • Intra nasal: Febrile seizures ○ In children
Diazepam	• Has coronary dilating property • Treat MI

Flunitrazepam 01:02:34

- Brand Name: Rohypnol
- Tasteless and colourless
- Misused - Mixed in the drinks
- Side effects: Sedation, Amnesia
- Misused as Date Rape drug
  - **Mnemonic:** AKBar GF
    → Alcohol
    → Ketamine
    → Barbiturates, benzodiazepines
    → γ hydroxybutyric acid
    → Flunitrazepam

Insomnia

01:05:14

- Chronic insomnia: >3 weeks
  - Anxiety is also present
- Transient insomnia: <3 weeks
  - Due to
    - → Jet lag
    - → Anxiety
    - → Sleep onset

Sleep cycle

- Wake Sleep: Sleep latency time
- Phases:
  - Non rapid eye movements: 1, 2, 3
  - Rapid eye movements
- Ideal drug for insomnia: Reduce sleep latency time
  - Should not interfere with sleep cycle

Drugs for insomnia

Barbiturates	• Not used • Causes maximum sleep cycle distortion ○ Increase the duration of NREM 2 ○ Decrease the duration of NREM 3 and REM ○ Frequent night awakening, nightmares → Rebound insomnia, hangover
Benzodiazepines	• Less sleep cycle distortion
Atypical benzodiazepines	• Other Name: Z drugs • DOC: Insomnia ○ Least sleep cycle distortion
Melatonin	• Non addictive drugs

1. Atypical benzodiazepines

01:11:20

- Other Name: Z drugs
- Benzodiazepines acts on α and γ subunit of GABA-A receptors
  - α_1: Produce sedation
    - → Treat insomnia
  - α_2: Muscle relaxant
    - → Treat seizures
- Z drugs Only act on α_1 γ subunit
  - Produce sedation
  - Treat insomnia
- Lack muscle relaxant effect and anti-seizure activity
- It includes
  - Zopiclone: Longest acting
    - → More sleep cycle distortion
  - Zolpidem
  - Zaleplon: Shortest acting
    - → Less sleep cycle distortion

- DOC: Insomnia
  - Chronic insomnia
  - Transient insomnia
  - Sleep onset insomnia
  - Jet lag (Off label use)
    → DOC: Ramelteon
- Side effect: Highly addictive
- Flumazenil (Antidote)-Atypical benzodiazepine, and benzodiazepine
  - Blocks α γ junction

2. Melatonin 01:16:30

- Also recommended in insomnia
- Non addictive drugs
- Dark: Increased melatonin: Sleep
- Light: Decreased melatonin: Awake
- Sleep wake cycle: Circadian rhythm

Dark
↓
Retina contain melanopsin pigment
↓
Optic nerve reaches the pineal gland
↓
Increased secretion of melatonin
↓
Induce sleep

- Drugs
  - **Mnemonic:** RAT

Ramelteon	• MT1 and MT2 receptor agonist
	• Treat insomnia
	  ○ Shift or night workers
	  ○ Elderly
	  ○ Jet lag
	• Metabolism: CYP1A2
	• $T_{1/2}$: 2hrs
	• Side effect: Somnolence (Excessive daytime sleepiness)

Agomelatine	• MT1 and MT2 receptor agonist + 5HT2C antagonist • Treat insomnia and depression
Tasimelteon	• Maintain circadian rhythm in blind people

3. Miscellaneous drugs for insomnia 01:21:56

- New drugs: Suvorexant, Lemborexant
  - Orexin antagonists
- 1st generation antihistamines
  - Has sedative action
  - Drug: Promethazine
- Mirtazapine, Mianserin: Antidepressant
  - Blocks α2 receptors in brain
  - Produce sedation
  - Used for depression + insomnia

39 ALCOHOLS

- **3 types**
  - Ethanol (can be consumed)
  - Methanol (wood spirit)
  - Ethylene glycol (used as solvent in industries and antifreeze agent) } Highly poisonous
- Alcohol is Metabolized or degraded by Dehydrogenase enzyme in liver

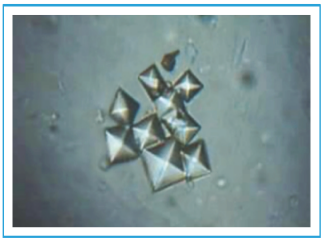
Methanol and Ethylene Glycol

00:01:56

Methanol and Ethylene glycol
↓
In liver
↓
Alcohol dehydrogenase enzyme Converts them to aldehyde
↓
Methanol to formaldehyde
↓
Ethylene glycol to glycol aldehyde
↓
These aldehyde are acted upon by aldehyde dehydrogenase and convert into acids
↓
Formaldehyde Converts to formic acid
↓
Ethylene glycol Converts to glycol acid + oxalic acid

- Formic acid, glycolic acid and oxalic acid-- Highly neurotoxic
  - **Leads to**
    → Retinal damage
    → Can Cause permanent blindness
  - Can also cause parkinson's disease
  - May cause death due to respiratory suppression

- **Ethylene glycol poisoning** 00:04:58
  - Oxalate Crystal in urine- (not seen with Methanol poisoning)
  - Renal stones
  - Envelope shaped crystals



- Fomepizole
  - Alcohol dehydrogenase inhibitor
  - Used in Methanol and Ethylene glycol poisoning

- Disulfiram
  - Aldehyde dehydrogenase inhibitor
  - Used in ethanol addiction

Treatment of Methanol and Ethylene glycol poisoning – (Mnemonic: SHAFE) 00:06:48

- **Sodium bicarbonate:** To treat high anion gap metabolic acidosis
- **Hemodialysis:** Best and effective treatment
- **Antidote**
  - Fomepizole -Orphan drug (not widely available)
- **Folinic acid**
  - Neuroprotective effect - Removes harmful acids that are produced
- **Ethanol**
  - If fomepizole is not available
  - Saturates dehydrogenase enzyme in liver
  - Oral and IV

Ethanol 00:09:54

- Causes alcohol addiction
- In high amounts produce happy feeling and pleasure
- If Alcohol consumption is continued tolerance may occur
- This leads to increase in dose of alcohol consumption - Leads to dependence
  - If alcohol is not available withdrawal symptoms are seen
    - → BP and HR increases
    - → Hyperexcitability
    - → Delirium tremens
- Long term Alcohol consumption damages vernix area of brain
  - Alcohol causes thiamine deficiency
  - Thiamine is important for vernix
  - Vernon damages - Leads to korsakoff's Psychosis

Treatment

- Manage acute withdrawal symptoms
  - **Delirium tremens:** IV benzodiazepine (diazepam)
    - → Not safe in liver disease
    - → If liver disease present - Lorazepam or oxazepam can be used
  - **Korsakoff Psychosis**
    - → Antipsychotic
    - → Long term treatment with thiamine
  - High BP and tachycardia
    - → Beta blocker: Propranolol
    - → Clonidine
- Maintenance to prevent another episode of withdrawal
  - DOC: Chlordiazepoxide - long acting benzodiazepine
  - If liver disease present: Lorazepam or oxazepam
- Prevention of relapse (abstinence to alcohol intake)
  - **Anti-craving drug:** Naltrexone + acamprosate
    - → Naltrexone: Opioid antagonist
    - → Acamprosate: NMDA receptor antagonist

- **Deterrent** (fear-inducing in the patient to take alcohol)
  - → Drug: Disulfiram
  - → Brand name: Entabuse
- **Off label anti-craving- non approved drugs**
  - → Topiramate
  - → Gabapentin
- **Off label deterrent: No approved antibiotic drug-** Metronidazole

Disulfiram 00:19:40

- Inhibits aldehyde dehydrogenase enzyme

Ethanol
↓
Converts to acetaldehyde by alcohol dehydrogenase
↓
Aldehyde converts to acetone acid by alcohol dehydrogenase

- Ethanol consumption after disulfiram use
  - Acetaldehyde Accumulates in the body
  - Produces harmful symptoms
    - → Nausea and vomiting
    - → Abdominal pain
    - → Chest pain
    - → Flushing
    - → Hypotension (can lead to death as well)
- Absolutely contraindicated in active drinkers
- Given only to maintain abstinence
- At Least gap of 12 hours of alcohol stoppage to start disulfiram
- Drugs showing disulfiram like action
  - Absolutely contraindicated in active drinkers
  - **Drugs** (mnemonic: CGMP)
    - → **C**hlorpropamide
    - → Cephalosporins (mnemonic: PMTX)
      - Cefo(p)erazone
      - Cefa(m)andole
      - Cefo(t)etan
      - Cefo(x)itin
    - → **G**riseofulvin
    - → **M**etronidazole
    - → **P**rocarbazine

Important Information

- Cephalosporins → C/I in active drinkers d/t presence of methyl tetrazole thiol (MTT) ring

40 OPIOIDS

- Natural alkaloids derived from the capsule of poppy plant (Papaver somniferum) 00:00:05
- **Two types**
  - Analgesics: Best painkillers
    - → Morphine: Full agonists of mu receptors.
    - → Codeine or methyl morphine
  - Non-analgesics (mnemonic:PNT)
    - → **P**apaverine is PDE inhibitors, Vasodilation in Peripheral vascular disease
    - → **N**oscapine: Antitussive or cough suppressant
    - → **T**hebaine: No use
- Natural opioids are known as opiates
- Endogenously produced opioids act on body cells.

Opioid Receptors Physiology 00:02:49

- Gi type of GPCR - Mu,Kappa,Delta Receptors
- Recently the 4th receptor was discovered: Orphanin/FQ - No use.

Mu	Kappa	Delta
Endogenous opioid acting on the receptor: Endorphins or endomorphin	Endogenous opioid acting on the receptor: Dynorphin	Endogenous opioid acting on the receptor: Enkephalins

Action: (SACRUM No GAP)
• **S**edation
• **A**nalgesia: Pain relief at all levels
  ○ Spinal: Substantia gelatinosa
  ○ Supraspinal levels: Pain associated with bad emotions like crying, stress and anxiety.
  ○ Decrease pain perception.
• **C**onstipation, cough suppression
• **R**espiratory depression (Cause of death due to overdose)
• **E**uphoria
  ○ Opioids are highly addictive drugs
• **M**iosis: Pin point pupil, as it stimulates EDW nucleus → Oculomotor nerve → Eye
• **N**ausea and vomiting → + CTZ
• **G**allstones/Biliary colic
• **A**bdominal colicky pain due to the spasm of GIT muscles (Sphincters)
• **P**rolactin ↑↑↑
	Same as Endorphin, except that it causes dysphoria (Psychosis like symptoms) and diuresis (↓ ADH → ↑ Urine secretion)	• Mainly produces supraspinal analgesia.
		• No drugs, as it may leads to convulsions
		• **Cause of death:** Respiratory depression
		• Constipation

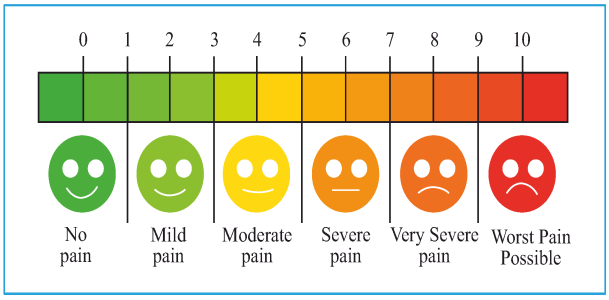
- Morphine is a full agonist at Mu receptor

Opioids

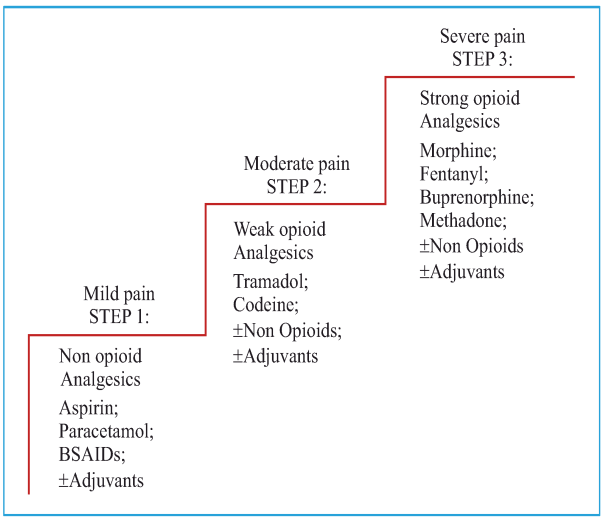
00:11:09

- **Use:** Most effective pain killer or analgesics.
- **DOC:** Moderate to severe pain
  - Cancer pain
  - Crush injury
  - Post OP pain
  - Fractures
- **Mild Pain-**NSAIDS- Aspirin,Paracetmol.Diclofenac
- C/I of Opioids
  - Morphine: Not given in colicky pain, Example: Biliary colic
  - Head injury
    → Reason: Opioids produce respiratory depression → ↑ CO_2 → Vasodilation in the brain → ↑ CSF production → ↑↑ ICP → Compress the brain.
    → Hyperventilation decreases the CO_2 levels and thus ICP decrease.
    → Interfere with Glasgow coma scale assessment
- WHO stepladder of Pain
- **VAS -** Visual analogue scale

00:16:13



- **Pain is classified into**



  - Mild: 1-3
    → **T/t:** NSAIDS
  - Moderate: 4-6
    → **T/t:** Low potency opioids, like tramadol, codeine
  - Severe: 7-10
    → **T/t:** High potency opioids, like morphine, pethidine, fentanyl

PYQ: FMGE2019

Drugs in Opioids

00:18:46

- Mu acting Opioids: MCP FMT
  - Morphine: 1 potency
  - Codeine: 1/10th potency
  - Propoxyphene: 1/8th potency
  - Fentanyl group: >100 times potency
  - Methadone
  - Meperidine
  - Tramadol and Tapentadol: 1/3rd potency
- Mixed acting Opioids: Acts on all opioid receptors.

Important Information

- Least potent (Max dose is required to produce analgesic effect): Codeine
- Most potent (Min dose is required to produce analgesic effect): Sufentanyl.

Note:

- Mild pain: NSAIDS → Aspirin, paracetamol, and diclofenac.

1. Morphine

00:21:42

- **Uses**
  - Analgesic
  - MI
  - Acute Left Ventricular Failure /Pulmonary edema
    → Cardioprotective effect: ↓ HR → Vagomimetic effect → ↓ Oxygen demand → Used in MI.
    → Venodilation → ↓ Preload → used in MI and LVF
- Opioids C/I in MI
  - Pethidine , pentazocine → they increase HR and oxygen demand of the heart.
- **P/K**
  - Morphine is active drug, when enters in the body it converts into
    → Morphine 6 glucuronide: Major form, produces analgesic effect.
    → Morphine 3 glucuronide: Minor form which can cause seizures or convulsions
      – Mostly produced in children.
- **Opioids C/I in renal failure**

00:26:26

  - Pethidine
  - Codeine
  - Morphine

  } ↑ Seizures
- **Route of administration**
  - Oral
  - Very fast acting group: Given in acute pain
    → IV
    → S/L
  - Transdermal: Long acting, given in chronic cancer pain.
  - Intrathecal: Inhibit vasomotor centre → ↑ Hypotension
  - Not given by intranasal/nasal spray, as it causes addiction.
- Oral/IV form of morphine produces miosis as it activates EDW in the brain, but if given via eye drops it doesn't cause miosis as the iris doesn't contain opioid receptors.

2. Diacetyl Morphine (Heroin)

00:29:45

- Modification of morphine
- Semi-synthetic derivative

- 10 times more potent analgesic
- Smugglers are called Heroin or brown sugar or smack.
- Heroin + Cocaine = Speed balls.
  - Cocaine prevents sleep so that the intense pleasure of opioids can be felt.

3. Codeine 00:31:43

- Inside the body it is converted into morphine by CYP2D6.
- Least potent analgesic drug: $1/10^{th}$ potency when compared to morphine, but equally antitussive (Suppress cough Centre)
  - Given in dry cough and allergic cough

Opioids as COUGH Suppressants (Antitussives)-Morphine And Codeine 00:33:03

- Morphine and semi-synthetic derivatives like
  - Oxymorphone
  - Hydromorphone
  - Levorphanol PYQ: INICET 2021
- Codeine and semi-synthetic derivatives like
  - Oxycodone
  - Hydrocodone
  - Pholcodine
- Cough abuse or misuse is more common due to their addictive nature.
- Non-addictive antitussives
  - Dextromethorphan - NMDA antagonists
  - Noscapine - Sigma agonist

Fentanyl Group

- Fentanyl ~ 100 times more potent
- Remifentanyl ~ 50 times more potent
- Alfentanyl ~ 50 times more potent
- Sufentanyl ~ 1000 times more potent: Most potent and maximum protein bound

4. Fentanyl 00:36:53

- Highly lipid solubility
  - Redistribution into fats
- Given by all routes except oral (d/t high first pass metabolism in liver)
  - Transdermal patch: Chronic cancer pain
  - Sublingual (Buccal or lozenges): Acute pain
  - Epidural/Spinal injection: Spinal analgesic
- Rare S/E: Wooden Chest Syndrome (Truncal rigidity)

Extra Point: Fentanyl + Droperidol (Neuroleptic drug) → Neurolept analgesia, if added nitrous oxide → Neurolept anaesthesia.

Important Information

- Longest acting opioid: Methadone

Remifentanil

- Shortest acting opioid
- Metabolised by plasma esterase enzyme, same like esmolol, which is also a shortest acting beta blocker.

- **Uses**
  - Day care surgeries
  - Total intravenous anaesthesia

Important Information

- GA used in day care surgeries and total intravenous anaesthesia: Propofol, as it doesn't have pain relieving acting it is combined with remifentanil.

5. Pethidine (Meperidine) 00:43:43

- Safest drug in pregnancy
- Post anaesthetic shivering, to stabilise the temperature centres (DOC)
- Pro-Drug, converted into;
  - Meperidine: Active form of drug
    → Produce opioid-like effects.
    → Converted through MAO-A enzyme
  - Nor-pethidine: Toxic form, produces seizure.
- It is Mu agonist + Anticholinergic effect (Atropine) → ↑ HR → Tachycardia, C/I in MI
- Relax GIT sphincters: Least risk of colicky pain.
- Never be combined with MAO inhibitors
  - It inhibits the MAO-A enzyme, producing more nor-pethidine, which causes seizures.
- C/I in renal failure: Nor-pethidine, if not excreted via urine → Seizures.

6. Methadone 00:47:53

- Mu agonist + NMDA antagonist
- **Action starts in**
  - Oral: 10 to 20 minutes
  - IV: 30 to 60 minutes
- Longest Acting opioid (40 hours)
- **Use:** Opioid deaddiction (Prevent withdrawal), as it lacks intense pleasure.
- Drugs approved for opioid deaddiction: (mnemonic: BMT)
  - Buprenorphine: Safer, less risk if causing respiratory depression.
  - Methadone: Most effective
  - Tramadol
- **S/E:** ↑ QT prolongation.

7. Tramadol and Tapentadol 00:51:01

- Mu agonist
- SNRi: ↑ Levels of S/NE.
- Weak analgesics: Moderate pain
- Paracetamol + Tramadol = Moderate pain
- S/E:
  - Nausea and vomiting as it activates the vomiting centre in the brain.
  - Serotonin syndrome, when combined with MAO inhibitors
    (Serotonin degraded by MAO enzyme, which further increases its levels)

Important Information

- Drugs not to be combined with MAO inhibitors
  - Pethidine → Seizures
  - Tramadol → Serotonin syndrome

Mixed Acting Opioids: Acts on any three receptors

00:53:34

1. Partial Kappa Agonist + Mu Antagonist: PNB

- Pentazocine
- Nalorphine
- Butorphanol
  - Only intranasal opioid, and is used in migraine headaches.
- **S/E:** Dysphoria or psychosis as it is a kappa agonist.
- **C/I:** Opioid deaddiction, as it is a Mu Antagonist
  - Precipitates withdrawal symptoms

2. Pure Kappa Agonist

- **S/E:** Dysphoria or psychosis
- **Drugs**
  - Nalfurafine: Uremic pruritus/pain in CKD
  - T/t: Diarrhoea in IBS
    - → Fedotozine
    - → Eluxadoline
    - → Asimadoline

3. Partial Mu Agonist + Kappa Antagonists

- **Buprinorphine**
  - Used for opioid deaddiction
  - Less risk of causing respiratory depression PYQ: INICET 2023
  - Binds to the mu receptor irreversibly, and hence, its action cannot be overcome by naloxone.
- **Dezocine**
  - **IV analgesic:** Faster acting than morphine.
  - Less risk of causing respiratory depression/Addiction
    - → **Reason:** Partial Mu agonist.

4. Pure Antagonists

- Competitive blockers of mu/kappa/delta receptors.
- Naloxone: IV, not absorbed via oral.
  - **DOC:** Antidote for morphine or opioid poisoning.
- Naltrexone: Oral drug to prevent relapse who were opioid addicted.
  - **S/E:** Hepatotoxic drug
- Nalmefene
  - Oral or IV
  - Liver safe
- **New drugs**
  - Naloxol
  - Naloxegol
  - Nalmidene

Opioid Overdose Symptoms

01:01:35

- **Symptoms of opioid poisoning**
  - Sedation
  - Dry secretion
    - → Eye/mouth
    - → Urinary retention
    - → Constipation

- Miosis: Pin point pupil
- Respiratory depression
- Convulsions

- **Symptoms of opioid withdrawal- By Naloxone**
  - Opposite to poisoning symptoms
  - Excitable
  - Increases secretion
    → Lacrimation
    → Salivation
    → Mydriasis
    → Increases in respiration (Yawning)
  - DOESN'T Produce convulsions

Important Information PYQ: NEET PG 2023

- In organophosphate poisoning: All the secretions of the body increases with pin point pupil.
- Naloxone doesn't produce convulsions

- Tolerance does not develop to 3 effects of opioids
  - Constipation
  - Convulsions
  - Constructed pupil (Meiosis)

Opioid Addiction

Psychiatry 01:05:04

Acute overdose/poisoning → IV Naloxone (Antidote)
↓
Maintenance (Detoxification phase: To prevent withdrawal)
3 opioids Bupernorphine,Methadone,Tramadol >> Non Opoids- Clonidine, Lofexidine
↓
Prevent relapse (Abstinence), DOC: Oral Naltrexone

Drugs used in the maintenance phase

- Opioids: BMT: Buprenorphine, methadone and tramadol are used
- Nonopioids: Clonidine and lofexidine.

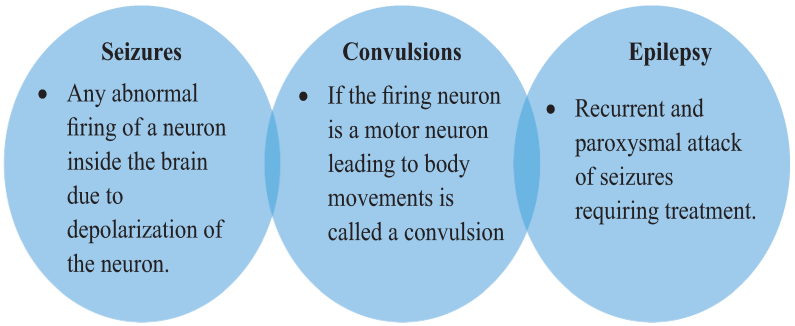
Opioids Used in Diarrhoea 01:08:06

- Anti motility drugs
- Loperamide
- Diphenoxylate
- Racecadotril

Treatment of Opioid Induced constipation

- **MOA:** Block opioid receptors in GIT.
- **Drugs**
  - Alvimopan: Mu opioid antagonist
  - Acts on any three receptors and are not absorbed orally but block opioid receptors in GIT.
    → Oral naloxone: Blocks local receptor
    → Methylnaltrexone
    → Nalmedene
    → Naloxol
    → Naloxegol

41 ANTI EPILEPTIC DRUGS



00:02:15

Management of Epilepsy

Acute seizure
- No treatment is required

Status epilepticus
- An acute seizure lasting for >5 mins and requiring treatment with IV antiepileptic drugs

For maintenance
- Oral anti-epileptic drugs are given for a minimum of 2 years.

Seizure free
- If the patient is seizure-free for 2 years the drugs are tapered slowly.
- Stopping anti-epileptic drugs suddenly may lead to rebound seizures - Most common cause of status epilepticus

Types of Epilepsy

Generalized Epilepsy
- The neurons of both the hemispheres are firing leading to loss of consciousness.

Focal Epilepsy
- The neurons of only one hemisphere are firing and in most cases, there is no loss of consciousness
- **First line drug**
  - Lamotrigine
  - Oxcarbazepine, Eslicarbazepine
  - Carbamazepine
  - Phenytoin
  - Levetiracetam

Generalized Tonic-Clonic Seizures
- Also called Grand mal epilepsy
- **DOC:** Valproate/ Lamotrigine

Absence seizures
- No convulsions
- Also called Petit mal epilepsy
- Only diagnosed based on EEG **(3 Hz wave spike pattern)**
- **DOC:** Ethosuximide/ Valproate/ Lamotrigine

Other types
- Atypical absence seizures- **< 2.5 Hz wave spike pattern**
- Tonic seizures
- Atonic: Loss of muscle tone
- Myoclonic seizures
- **DOC:** Valproate/ Lamotrigine/ Topiramate

Miscellaneous Epilepsy Syndromes

00:12:32

Lennox Gestaut syndrome

- Mainly occurs in children with mental retardation
- Most commonly seen seizures- Myoclonic, Tonic, and Atonic
- First-line drug- Valproate
- Clobazam is added if the seizures are not controlled by Valproate
- Orphan drugs- Rufinamide is added if there is still no control and Felbamate is a last resort drug.

Dravet's syndrome

- Severe myoclonic epilepsy in infancy
- DOC: Valproate
- **No response:** Clobazam is added
- **Still no response:** Stiripentol is added (Orphan drug)

Infantile spasm

- Also known as West syndrome/Hypsarrhythmia
- **Isolated infantile spasms**
  - Occur occasionally
  - DOC: ACTH hormone +/- glucocorticoids-Through negative feedback suppresses corticotropin- releasing hormone
- **If associated with tuberous sclerosis**
  - Lifelong seizures and lifelong treatment is given
  - DOC: Vigabatrin

Febrile seizures

- Seen in children with high-grade fever
- DOC: Rectal diazepam
  - Both for treatment and prevention
  - Intranasal spray of midazolam - Recently developed
  - Intranasal diazepam is also available

Juvenile myoclonic epilepsy

- Also known as Janz syndrome
- **DOC:** Valproate > Lamotrigine > Topiramate
- **Valproate:** Most teratogenic
- **In pregnancy:** DOC is levetiracetam (Safest in pregnancy)

Important Information

- Phenytoin and Carbamazepine are contraindicated in myoclonic epilepsy as they aggravate the condition.

Management of Epilepsy in Pregnancy

00:22:19

- A known case of seizures on medication and getting pregnant.
  - Anti-epileptic drugs should not be stopped to prevent rebound seizures
  - Folic acid dose should be increased to 10 times
  - Add vitamin K in the last trimester
- A seizure-free female gets pregnant and then develops seizures
  - Start levetiracetam or lamotrigine
  - Safe in pregnancy
  - Never start with valproate

Drugs	Pregnancy	Lactation
Valproate	Most teratogenic	Least secreted (safe)
Levetiracetam	Least teratogenic	Most secreted (unsafe)

Status Epilepticus

00:26:48

Early status epilepticus: Seizures not controlled in the 1st 5 mins.
- **Overall DOC:** IV Lorazepam (0.1 mg/ kg)
- **Other benzodiazepines**
  - IV clonazepam
  - IV clobazam
  - IV or IM midazolam

↓ Still no control

Add IV phenytoin or valproate or levetiracetam

↓ Still no control

Early refractory status epilepticus: Seizures lasting for > 30 mins
- Categorised either as GTCS or focal or other types of generalized seizures
- **If GTCS:** IV propofol or midazolam
- **Focal or other types:** Phenytoin or valproate or levetiracetam

↓ Still no control

IV phenobarbitone is added

↓ Still no control

Late refractory status epilepticus: Seizures Lasting for >48 hours
- Give general anesthesia: Isoflurane/ Desflurane/ Inj. Ketamine
- Muscle relaxants: Verapamil/Magnesium sulfate/Lignocaine
- **Surgery:** Remove damaged part of brain
- Hypothermia and keto diet are other measures

- **Lamotrigine:** C/I due to Steven-Johnson syndrome (hypersensitivity reaction)
- Preferred to give fos-phenytoin is a preferred drug rather than phenytoin as it is faster acting.

Classification of Antiepileptic drugs

00:33:34

- Anti-epileptics act by inhibiting neuron depolarization.

In a neuron at rest - (-)ve charge inside the cell and (+)ve outside the cell

← Hyperpolarization of cell by promoting entry of Cl^-

→ Hyperpolarization of cell by promoting efflux of K^+

↓

Depolarization

↓

Due to the entry of Na^+ and Ca^+

↓

Releases glutamate (excitatory neurotransmitters)

↓

Responsible for seizures by acting through the NMDA, AMPA and kinase receptors

- **Mechanisms to block depolarization**
  - Block sodium entry
  - Block calcium entry
  - Promote chloride entry
  - Promote potassium efflux
  - Inhibit the release of glutamate (levetiracetam)
  - Block glutamate receptors

Sodium Channel Blockers

00:37:22

- These block use-dependent voltage-gated sodium channels and they block at open-state.
- **Drugs**
  - Phenytoin: Exclusive sodium channel blocker
  - Carbamazepine: Exclusive sodium channel blocker
  - Valproate
  - Topiramate
  - Lamotrigine
  - Lacosamide: Produce inactivation of sodium channel
    - → Rufinamide
    - → Zonisamide

1. Phenytoin

Introduction

- Also called diphenylhydantoin
- Non-sedative anti-epileptic (no CNS depression due to least or no activity on GABA)

Uses

- First-line drug for focal seizures
- Second-line drug for GTCS

Contraindications

- Myoclonic seizures
- Absence seizures (no action on T-type calcium channel)

Pharmacokinetics

- RoA: Oral or IV (50 mg/kg)
- Fos-phenytoin (made from phenytoin)
  - More water soluble and can be given faster
  - Less risk of thrombosis
  - Preferred in status epilepticus
  - Dose: 150 mg/kg
  - More risk of arrhythmia like asystole
- Albumin bound
- All AEDS are acidic
- All AEDS displace each other from albumin - Can cause toxicity
- Metabolized by CYP2C9
  - If the dose is increased, CYP2C9 concentration gets saturated and shows zero or pseudo-zero order kinetics
- Narrow therapeutic index drug: Requires TDM
  - Normal blood level of phenytoin: 10 to 20 mg/ml
  - >20 mg/ml: Toxicity

Adverse effects

At high dose (preventable)	At normal dose (non-preventable)

• Cerebellar neurotoxicity
  ○ Nystagmus
  ○ Ataxia
  ○ Diplopia
  ○ Slurred speech
• Cerebral Neurotoxicity - Psychosis
• Cardiac toxicity - Arrhythmia, asystole
	• Hyperplasia of gums (most common)
	• Hirsutism
	• Heavy weight (obesity)
	• Hyperglycemia
	• Hypersensitivity: Indication to stop phenytoin and replace with valproate
	• Hamper vitamin absorption from GIT
	  ○ Vitamin K (cause osteomalacia)
	  ○ Vitamin D (cause osteomalacia)
	  ○ Folic acid (Megaloblastic anemia)
	• Hodgkins like pseudolymphoma
	• Hydantoin syndrome in the fetus

Important Information

- Phenytoin and valproate can cause PCOD

Gingival hyperplasia

- **Drugs causing Gingival hyperplasia**
  - Phenytoin
  - Calcium channel blockers like Amlodipine
  - Cyclosporine
- **Treatment**
  - Good oral hygiene
  - Antibiotics: Erythromycin or Azithromycin

Hydantoin syndrome

- Teratogenic effect of phenytoin
- Causes
  - Microcephaly
  - Cleft lip and cleft palate
  - Hypoplastic phalanges

Therapeutic index of AEDs

- Antiepileptic drugs are narrow therapeutic index drugs

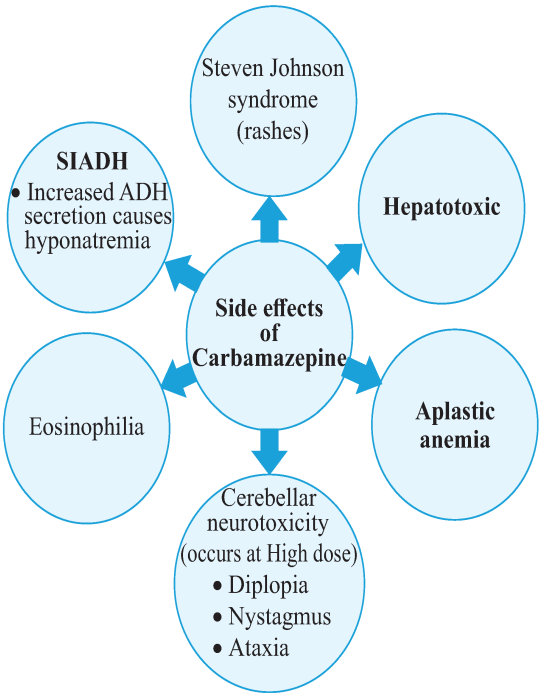
Drug	Therapeutic range
Phenytoin	10 to 20 mg/ml
Valproate	50 to 100 mg/ml
Phenobarbitone	15 to 40 mg/ml
Carbamazepine	4 to 12 mg/ml

AEDs in the treatment of neuropathic pain

- Neuropathic pain (neuralgia) occurs due to the excessive firing of the peripheral neuron
  - Trigeminal neuralgia: DOC is Carbamazepine

- Post herpetic neuralgia: Pregabalin or gabapentin
- Diabetic neuropathy: Pregabalin > Gabapentin
- **Other drugs**
  - → Phenytoin
  - → Lamotrigine
  - → Topiramate
- Valproate is not used due to its high toxicity.

2. **Carbamazepine** 01:02:00
   - The mechanism, uses and contraindications are the same as phenytoin
   - Also given in bipolar disorder treatment but phenytoin is not used
   - **Pharmacokinetics**
     - Overall safer drug than phenytoin
     - Enzyme inducer (increase CYP enzyme activity)
     - Autoinducer (own degradation)



Important Information

- All AEDs are CYP inducers except valproate
- Steven Johnson syndrome is caused by Carbamazepine, Lamotrigine and occurs in children
- SIADH is seen in old age people
  - Carbamazepine is also used in diabetes insipidus treatment
- Carbamazepine
  - Teratogenic and causes neural tube defects

- Oxcarbazepine (prodrug) and Eslicarbazepine (active) are modifications of Carbamazepine
  - Less CYP inducers
  - Longer-acting drugs
  - **Side effects**

→ Less risk of Steven Johnson Syndrome (Preferred in children)

→ More risk of SIADH (not preferred in old age)

- HLA typing is important to avoid the risk of hypersensitivity

Pharmacogenetic testing	
Drug	**HLA type**
Carbamazepine	HLA B* 1502
Allopurinol	HLA B* 5801
Abacavir	HLA B* 5701

3. **Lacosamide** 01:12:42

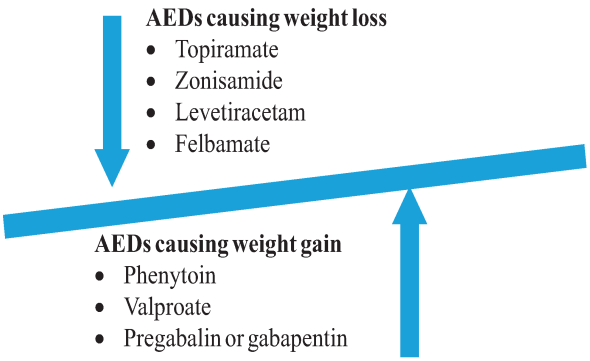
- 2nd line drug for focal seizures
- **MoA**
  - Produces slow inactivation of sodium channel
  - Inhibit the release of CRMP-2 (causes abnormal connections of neurons)
- **Side effects**
  - Increased risk of suicides
  - Blocks AV node
  - On ECG: Increased PR interval

4. **Rufinamide**

- Drug for Lennox Gestaut syndrome

Topiramate and Zonisamide 01:14:31

Mechanism of action	• Both drugs block sodium channels and have carbonic anhydrase inhibitor properties (like Acetazolamide) • **Topiramate:** Blocks glutamate receptors • **Zonisamide:** Blocks T type of calcium channel (Given in treatment of absence seizures)
Indications	• Both are approved as anti-obesity drugs
Side effects	• **In eyes:** Angle-closure glaucoma • **In kidneys**: Nephrolithiasis • **In blood:** Metabolic acidosis



Calcium Channel Blockers

01:19:00

- Blocks T-type calcium channel
- T-type calcium channel
  - Transient
  - Present in thalamic neurons
    - → Sensory neurons relay here and increased firing of these neurons causes absence seizures.
- **Drugs**
  - **1st line drugs**
    - → Valproate
    - → Ethosuximide
    - → Lamotrigine
  - **2nd line drugs**
    - → Zonisamide
    - → Levetiracetam
    - → Clonazepam
- **Drugs contraindicated in the absence seizures**
  - Phenytoin
  - Carbamazepine
  - No action on T-type calcium channel

- **Upper part**
  - Cortex (cortical neurons contain Na^+ channel)
  - Motor neurons come from here that are responsible for GTCS and focal seizures
- **Below cortex**
  - Thalamus (sensory part of the brain) is present
  - Responsible for absence seizures

- Drugs blocking sodium channels are beneficial in GTCS and focal seizures
  - Phenytoin
  - Carbamazepine
- Drug-blocking calcium channel - Beneficial in the absence seizures
  - Ethosuximide
- Drug blocking both sodium and calcium channels
  - Valproate
  - Lamotrigine

Valproate

01:22:55

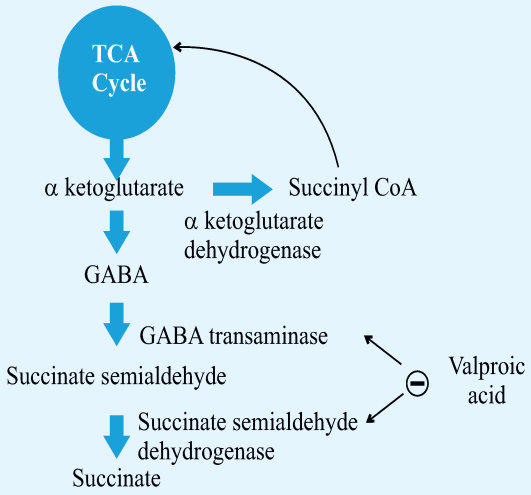
Blocks

- Sodium channels
- Calcium channels
- Promotes GABA action

Used in

- All types of seizures
- Bipolar disorder
- Migraine prophylaxis

Inhibits GABA degradation



Type of drug

- Sedative drug

Adverse effects

- **V**omiting and Nausea: To reduce this Divalproex sodium can be used
- **A**lopecia
- **L**iver toxicity (mainly in < 2 yrs age children)
  - Age-specific
  - Increased with carbamazepine
- **P**ancreatitis and PCOD (gender specific)
- **R**ash
- **O**besity
- High **A**mmonia levels: Hyperammonemic encephalopathy
  - Treated with L- carnitine
- **T**eratogenic (most) - Causes neural tube defects
- **E**nzyme CYP inhibitor

Spina Bida Oculta

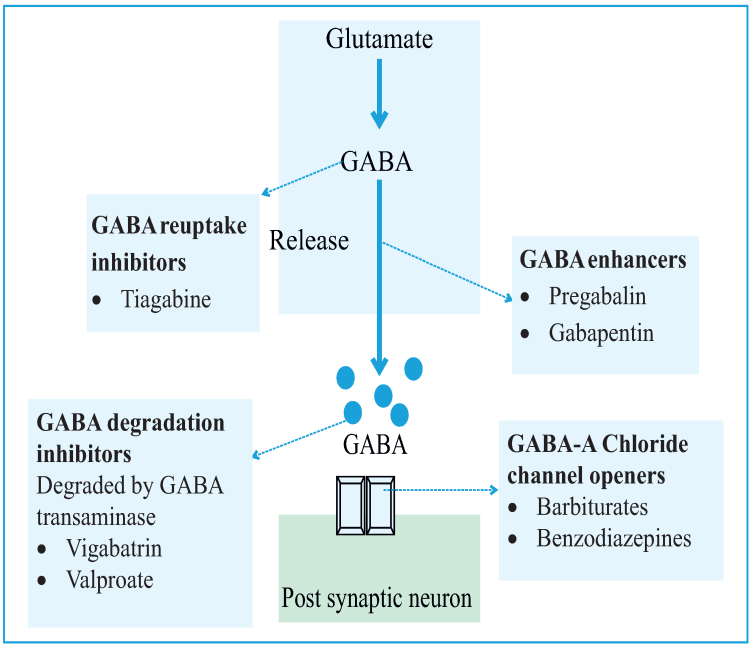
Ethosuximide

- Exclusively Block T type of calcium channel
- Only used in absence seizures
- Advantage: Not hepatotoxic
- Preferred in children
- **Side effects**
  - SLE-like symptoms
  - Bone marrow suppression

Lamotrigine

- All actions like valproate
- Given as 1st line drug in all types of seizures
- Approved for bipolar disorder
- Main side effect: Steven Johnson syndrome (rashes)
  - Seen when an IV fast injection is given
  - Common in children
- Contraindicated in Status epilepticus

Drugs Promoting GABA-A Chloride Channels 01:33:08



Important Information

- Any drugs that increase the levels of GABA are sedative and promote weight gain.

Benzodiazepines	Barbiturates

• Diazepam
• Lorazepam
• Clonazepam
• Clobazam
• Midazolam
	• Phenobarbitone
	  ○ Most preferred for neonatal seizures
	  ○ Also given in status epilepticus
	• Mephobarbital
	• Primidone
	• **Stiripentol**: Used in Dravet syndrome

Pregabalin and Gabapentin

- Promote GABA release
- Blocks P/N type of calcium channel
- Used in treatment of
  - Neuropathic pain
  - Focal seizures
  - Restless leg syndrome
  - Migraine

Tiagabine

- GABA transporter inhibitor
- New drug for focal seizures

Ganaxolone

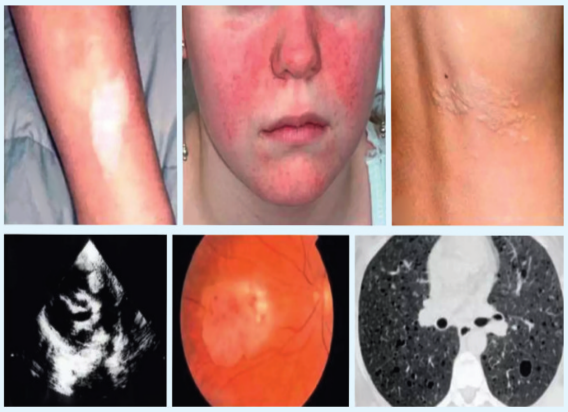
- New drug
- $GABA_A$ Cl^- channel agonist
- Approved for infantile spasm

Vigabatrin

- GABA transaminase inhibitor
- **Use**: DOC in infantile spasm associated with tuberous sclerosis (genetic)
- **Side effect:** Visual field contraction

Tuberous sclerosis

- Autosomal dominant
- Features
  - Hypopigmented macule on skin
  - Angiofibroma on face
  - Shagreen patch
  - Rhabdomyosarcoma
  - Hamartomas in retina
  - Lymphangiomyomatosis



Drugs inhibiting glutamate release

01:43:08

- Glutamate is an excitatory neurotransmitter and is stored in vesicles.

Levetiracetam

- Inhibits synaptic vesicle two-A (SV_2A) protein and inhibits the release of glutamate.
- **Additional properties**
  - Increases memory (Nootropic)
  - Antioxidant property (neuroprotective)
  - Blocks T type of calcium channel
- Recently approved in treatment of absence seizures as it blocks T-type Ca^{2+} channels.
- Safe in pregnancy
- No drug interactions (no action on CYP)

Brivaracetam

- Inhibits sodium channels
- Approved for focal seizures treatment

Piracetam

- Approved for Alzheimer's disease

Drugs blocking glutamate receptors

01:47:15

NMDA blocker: Felbamate

- Specifically approved for Lennox Gestaut syndrome
- Side effects
  - Aplastic anemia
  - Hepatotoxicity

AMPA blocker

- Perampanel
- Talampanel
- 2nd line drugs for focal seizures

Kinate blocker

- Topiramate

Potassium Channel Opener

01:48:50

- **Drug:** Ezogabine or retigabine
- Opens KCN/Q channel
- Efflux of potassium leading to hyperpolarization
- 2nd line drug for focal seizures
- New drug
- Specific side effects: Visual loss and blue pigmentation of skin

Cannabidiol

01:50:08

- Recently approved as AED
  - Approved in the treatment of
    - → Infantile spasm
    - → Lennox Gestaut syndrome
    - → Dravet's syndrome (>1 yr of age)

Important Information

- Drugs requiring regular eye checkups
  - Vigabatrin
  - Ezogabine
  - Topiramate

42 PARKINSON DISEASE AND OTHER DISORDERS

Parkinson's Disease

Medicine

Pathogenesis

1⁰ Parkinson's disease
- Idiopathic progressive neurodegenerative diseases
- Occurs in dopaminergic neurons in substantia nigra-pars compacta (SN-PC) of basal ganglia.
- Idiopathic cause
- Toxin causing Parkinson's disease: MPTP

2⁰ Parkinson's disease
- Drug-induced
- The drug blocks the dopaminergic receptor
- Dopamine levels are normal

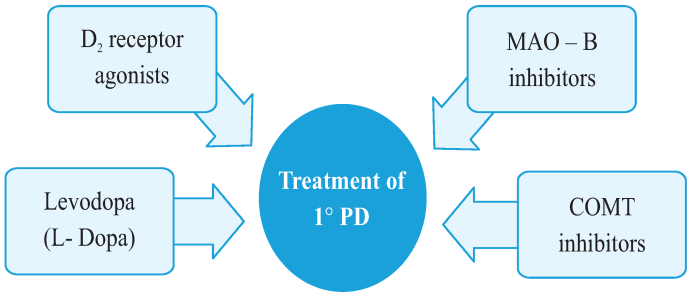
- **Imbalance**
  - In basal ganglia, decreased Dopamine leads to increased ACh
  - Imbalance causes increased muscle tone or dystonia.
  - Features - Functional impairment
    - → Rigidity
    - → Bradykinesia (Slow movement)
    - → Resting tremors
    - → Festinant gait

PYQ: FMGE 2022

- **Treatment**
  - 1⁰ PD: Drugs that increase dopamine levels
    - → Levodopa
  - 2⁰ PD: Anticholinergics

PYQ: NEET PG 2022
PYQ: FMGE 2021

00:05:37



Levodopa (L-Dopa)

00:08:15

Dopamine cannot cross BBB, but levodopa crosses BBB

↓

Levodopa enters neurons in the Gasal ganglia

↓

Converted into dopamine inside the neuron via Dopa decarboxylase

↓

Dopamine is released by the neuron and acts on the D_2 receptor

↓

The dopamine is degraded via MAO-B and COMT

- Levodopa is a prodrug
- Dopa decarboxylase is present in the brain as well as peripheral neurons
- Combining Levodopa with peripheral Dopa decarboxylase inhibitors like Carbidopa/Bensarazide prevents side effects of dopamine in the periphery
- Levodopa + Carbidopa = Synergism (BN: Syndopa)
- Levodopa is never combined with vitamin B6/pyridoxine
  - Vitamin B6/pyridoxine stimulates peripheral Dopa decarboxylase leading to increased peripheral conversion of the levodopa and increase peripheral side effects.

Important Information

- Pyridoxine is a cofactor for almost all decarboxylase enzymes.

- **Adverse Effects of Levodopa** 00:13:00
  - Abnormally increased levels of dopamine can cause side effects in the periphery and brain.
    → Peripheral side effects are reduced by Carbidopa but it increases the CNS side effects.

PYQ: INICET 2022

Nausea and vomiting (MC)
- Activates D_2 receptor in CTZ brain outside BBB.
- Treatment: Domperidone → Blocks D_2 receptor at CTZ

Postural hypotension
- Activates D_2 receptor in blood vessels → vasodilation.

Mydriasis
- Stimulates α-1 receptor in the iris.

Arrhythmias
- Stimulates β-1 receptors in the heart.

Peripheral — **CNS**

Basal ganglia: Dyskinesia
- Treatment: Amantadine, Levetiracetam

Cortex: Psychosis
- Treatment: Clozapine, Quetiapine, Pimavanserin

Medulla
- Hypersexuality and impulsive gambling

Contraindications to Levodopa

- Angle-closure glaucoma
  - Levodopa closes the iridocorneal angle and blocks the trabecular outflow.
- Melanoma
  - Levodopa increases the production of melanin pigment

Important Information

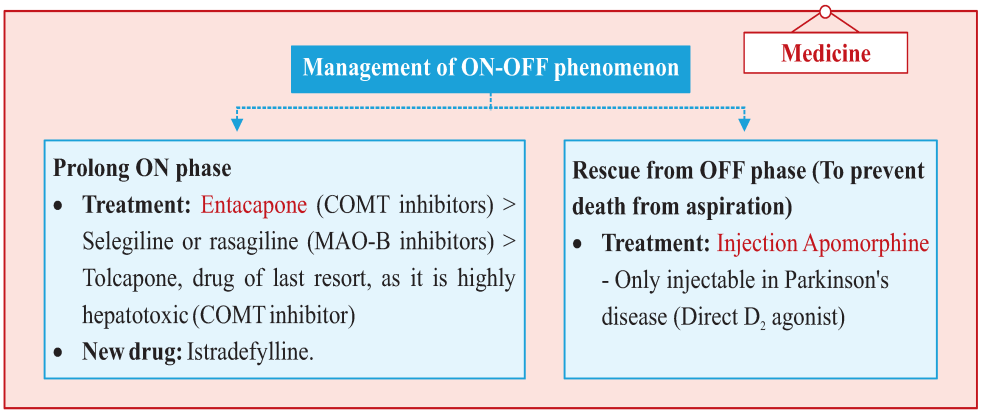
- Any drug-producing mydriasis is contraindicated in glaucoma.

- Levodopa in Parkinson's disease
  - DOC in Parkinson's disease
  - Most effective for functional improvement
  - Reduce all symptoms except resting tremors
  - To control resting tremor, anticholinergics (Benzhexol) are used.
  - It shows an on-off phenomenon

ON-OFF Phenomenon 00:22:50

- With time, the effect of levodopa reduces, as Parkinson's disease is a progressive neurological disorder.
- On - Improvement

- Off - Rigid
- As the neuron number decreases, the amount of levodopa converting into dopamine decreases →Time of action of dopamine.



COMT inhibitors 00:28:45

- Catechol O Methyl Transferase enzyme inactivates or degrades dopamine into O methyl transferase.
  - The drugs end with -capone.

Entacapone	Tolcapone	Newer
• Cannot cross BBB • Inhibits degradation in GIT and increases the absorption of levodopa. • Safer, given first	• Cross BBB • Inhibits degradation in GIT and brain, and increases the absorption of levodopa • Highly hepatotoxic: Drug of last resort	• Opicapone • Nitecapon

MAO Inhibitors 00:31:58

- Monoamine oxidase–B enzyme degrades dopamine into DOPAC (Neurodegenerative effect)

MAO – B Inhibitors (Irreversible)	MAO – B Inhibitors (Reversible)

• Selegiline
  ○ Treatment: depression (Transdermal patch)
• Rasagiline (Longer and potent)
• Uses
  ○ Used to prolong ON phase
  ○ Only neuroprotective drugs in PD
	• Safinamide

New Drug for ON-OFF Phenomenon

- Istradyfilline: Adenosine (A_2) receptor blocker
- Dopamine binding of the receptors increases → Prolonging ON phase

Amantadine

00:36:00

Mechanism of action

- Mainly for the treatment of levodopa – induced dyskinesia PYQ: INICET 2022
- Amantadine is an NMDA antagonist that blocks glutamate receptors and reduces excessive release of dopamine
- Glutaminergic neurons act on other neurons and cause the release of dopamine
- If blocked, prevent dyskinesia due to excessive release of dopamine

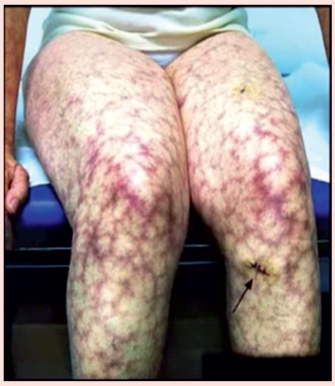
Uses

- Parkinson's disease
- Antiviral drug – effective for the treatment of influenza virus (Swine flu)

Side effect

- Vasodilation causes ankle edema and livedo reticularis (purple to brown, net-like pattern)

Medicine



Livedo reticularis

Important Information

- **Levitracetam:** Antiepileptic drug used in levodopa-induced dyskinesia.

Dopamine Agonists (D_2)

00:39:55

Ergots	Non-ergot derivatives
• Not used nowadays • Bromocriptine • Cabergoline • Long-term administration: Ergotism (dry gangrene of fingers due to ischemia) • But they are given in the treatment of prolactinoma	• Ropinirole (oral) • Pramipexole (oral) • Rotigotine: Transdermal or transcranial patch • Apomorphine: Injection ○ To rescue from OFF position • Less effective than levodopa • Used as first drug in mild PD • Side effects: like levodopa, but milder

Management of Parkinson's Disease

Medicine , Psychiatry

00:43:55

Mechanism	Drug
No functional impairment or asymptomatic	Seligiline or rasagiline (Only neuroprotective drug)
Functional impairment	Levodopa (DOC and most effective) >>> Mild PD (Ropinirole or pramipexole)
Inhibit peripheral degradation of levodopa	Carbidopa, Benserazide
Levodopa-induced dyskinesia	Amantadine, Levitiracetam
Prolong ON phase	Entacapone → MAO-B inhibitors → Tolcapone
Reduce OFF phase	Injection Apomorphine
Vomiting	Domperidone
Psychosis	Clozapine, quetiapine, pimavanserin
Resting tremors (levodopa is not effective)	Anticholinergics like Benzhexol are used.

Drug-Induced Parkinsonism

00:47:16

Pathophysiology

- Blockade of D_2 receptors in basal ganglia causing decreased dopamine and increased ACh.

Management

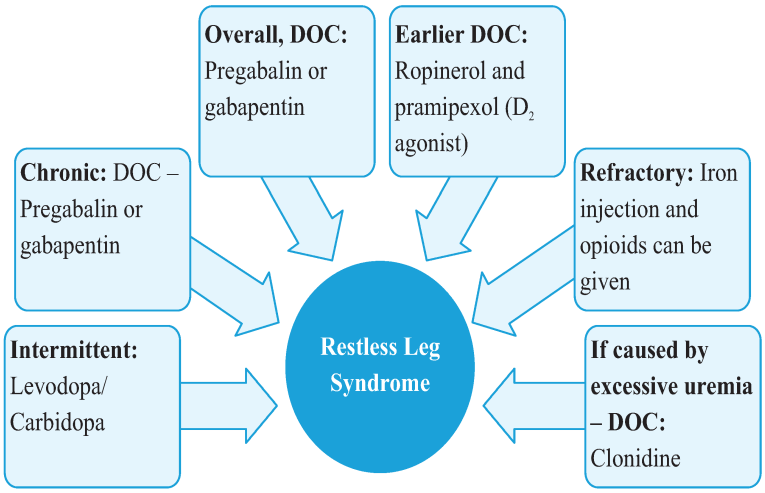
- DOC: Anticholinergics
  - Benzhexol (Trihexphenidine)
  - Benztropine
  - Biperidine
- Other classes
  - Antihistaminic drugs: Promethazine (Phenergan) and Diphenhydramine (Benadryl)

PYQ:NEET PG 2020

Etiology of drug-induced PD

- Antipsychotic (almost all)
  - Haloperidol
  - Risperidone
- Antiemetic
  - Metoclopramide

00:50:57



Huntington's Disease

00:52:53

Pathophysiology

- Due to degeneration of ACh neurons in basal ganglia, there is excessive dopamine and reduced levels of acetylcholine

Presentation

- Presents with excessive movements known as Chorea

Management

- DOC: Dopamine depletors (End with – benazine) – VMAT inhibitors
  - Tetrabenazine
  - Deu-Tetrabenazine (Longer acting)
  - Valbenazine
- VMAT-2 transporter is required for dopamine to enter the vesicles in the neurons. Inhibition of this transporter leads to dopamine degradation and dopamine not being released
- VMAT inhibitors not effective → atypical antipsychotic drugs added → not effective → typical antipsychotic drugs added (block D2 receptors)

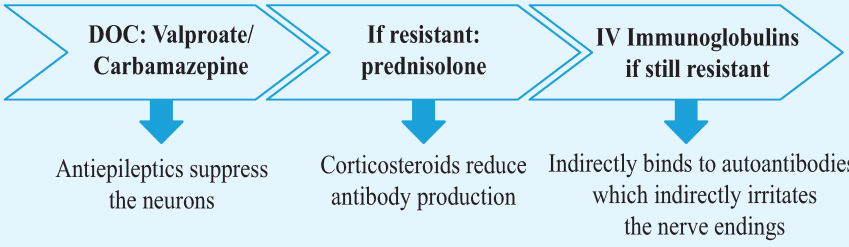
Rheumatic Chorea (Sydenham's Chorea)

00:56:37

Pathophysiology

- It is hyperimmune disease, excessive antibodies are produced against streptococcal antigens and these antibodies irritate the nerve ends and lead to chorea

Management



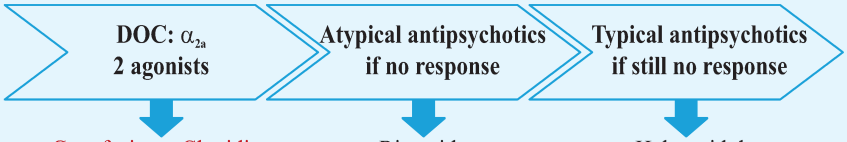
Tourette Syndrome (TIC Syndrome)

00:58:28

Presentation

- Multiple repetitive movement

Management



- **TIC + ADHD**
  - **DOC:** Guanfenacine > Clonidine or Atomoxetine (Antipsychotic)

Wilson's Disease

01:01:00

Inheritance

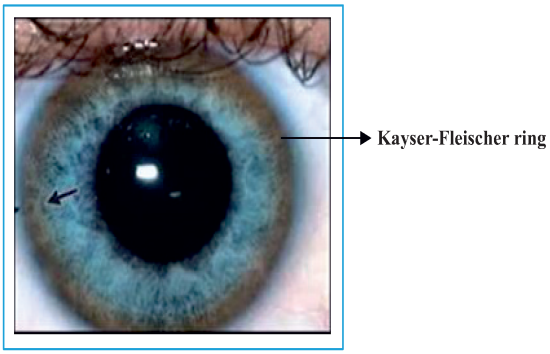
- Autosomal recessive

Pathophysiology

- Deficiency of ceruloplasmin (copper chelator)
- Free copper enters in organs and deposits to damage the organs
  - **Eyes:** Brown coloured ring (Keyser-Fleisher ring)
  - **Liver:** Cirrhosis
  - **Brain:** Parkinson's disease

Management

- Overall, DOC: Zinc (decrease copper absorption in GIT)
- If there is damage in organs – A copper chelator from outside is added
  - Liver damage: Trientene > Penicillamine > Liver transplant
  - Neurological damage: Tetrathiomolybdate



Important Information

- Penicillamine is also used in the RA, as an immunosuppressive drug.

Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease)

01:05:30

Facts

- Rare, neurodegenerative condition
- Stephen Hawking suffered from this disease

Management

- Neuroprotective drugs
  - Riluzole: NMDA antagonists
  - Edaravone: Antioxidant
- New drugs
  - Tofersen: RNA Anti-sense, binds with normal RNA and inhibits the formation of an abnormal protein (ALS→SOD-1 mutation)
  - Sodium phenylbutyrate

Retts syndrome

Progeria syndrome

Freidreich ataxia

Trofinetide
- Tripeptide of IGF-1.

Lonafarnib
- Tyrosine kinase inhibitor.

Omaveloxolone
- Antioxidant effect.

Multiple Sclerosis

Medicine

01:10:20

Pathophysiology

- Multiple sclerosis is an autoimmune condition, antibodies are produced against myelin basic proteins
- Damages myelin sheet, produced by oligodendrocytes of CNS neurons

Clinical features

- Fatigue or weakness
- Spasticity
- Gait abnormalities

Management

- Treatment of relapse (attack)
  - **DOC:** IV methylprednisolone
  - If not controlled: IV – Ig > Plasmapheresis
- Prolong remission (asymptomatic period)
  - Disease-modifying agents

Types of MS

According to McDonald's criteria

RRMS (relapsing-remitting multiple sclerosis)
- **DOC:** INF-β + Add other drugs

SPMS (secondary progressive multiple sclerosis)
- **DOC:** Mitoxantrone + Add other drugs

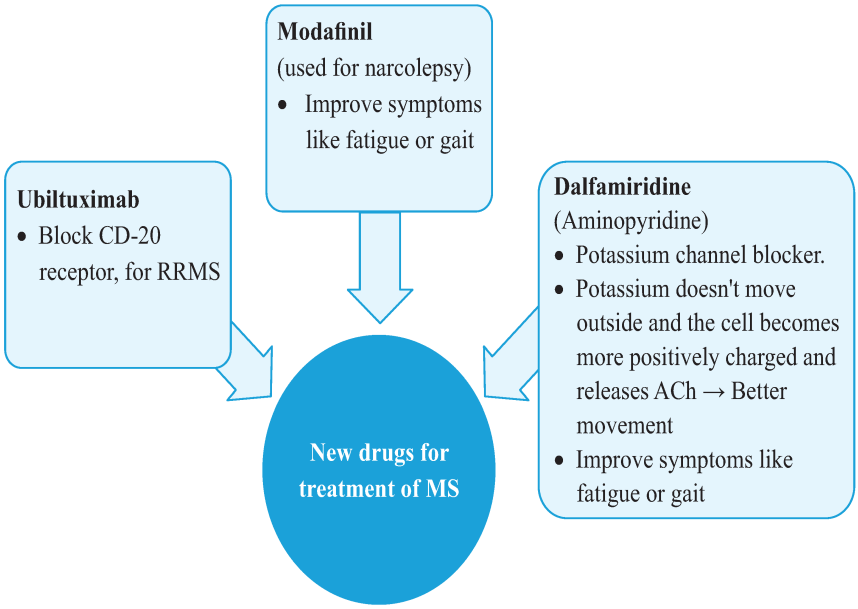
PPMS (primary progressive multiple sclerosis)
- Most dangerous, the patient dies within few weeks or months
- Only drug – Ocrelizumab

Disease Modifying Drugs for Multiple Sclerosis

- **Note: Mnemonic- GO FIND DAT CM**

Glatiramer Acetate	• Oral drugs with 4 AA (Glutamate, lysine, alanine, tyrosine) • Directly bind to circulating autoantibodies and prevent them from binding with myelin basic protein.
Ocrelizumab	• All monoclonal antibodies are given via injections • Block CD-20 on B-lymphocytes • Only drug approved for PPMS
Fingolimod, Siponimod, Ozanimod	• Oral drugs • Sphingosine receptor (present on lymphocytes) modulators, decreases the production of antibodies. • **Side effects:** Cardiotoxic, increases the risk of herpes zoster infection.
Interferon β	• Overall, DOC for MS • Generally, suppresses autoantibodies production • **Side effects:** Flu-like symptoms and Hypothyroidism. • Injectable as they're peptides
Natalizumab	• Injectables • Block integrin receptor, which is present on endothelial cells. ○ The WBC integrates with the integrin receptor and comes out via diapedesis and causes inflammation. • Inhibits migration of WBC • **Side effects:** Increase in risk of JC polyomavirus (Damages white matter of the brain) → Progressive multifocal leukoencephalopathy.
Di Methyl Fumarate	Inhibits nuclear factor 2 and decreases the production of antibodies through nuclei.
Daclizumab	Blocks CD-25 receptor
Alemtuzumab	Blocks CD-52 receptor
Teriflunomide	• Active form of Leflunomide (used in the treatment of RA) • Inhibits DHOD (Dihydro-orotate dehydrogenase) • Inhibit pyrimidine synthesis • Oral drug
Anti-cancer drug	• Kills lymphocytes and acts as an immunosuppressive drug. • Cladribine • Mitoxantrone

- Questionnaire for MS: EDSS (Extended disability status scale)
  - **Max improvement:** Mitoxantrone > Natalizumab



Neuromyelitis Optica or Devic's Disease

01:27:00

- Variant of MS involving eyes and spinal cord.
- DOC: Eculizumab - Block C5 complement and reduces inflammation
  - Also approved for the treatment of PNH (Paroxysmal nocturnal hemoglobinuria)
- **Sartralizumab:** Inhibits IL-6
- **Ineblizumab:** Inhibits CD-19.

43 ANTI PSYCHOTIC DRUGS

	Psychosis	Neurosis/ Anxiety disorder
Insight	• Absent	• Present

Types	• Schizophrenia
	• Mood disorder
	  ○ Mania
	  ○ Depression(unipolar)
	  ○ Bipolar disorder/ MDP
		• Generalized anxiety disorder
		• OCD
		• Phobias
		• Hysteria
		• Anorexia/ bulimia
		• Premenstrual tension syndrome (PMTS)

Treatment	• Antipsychotics are used in Schizophrenia
	• Mood stabilizers are used in MDP/BPD and Mania.
	  ○ Lithium
	  ○ Antiepileptics
	  ○ Antipsychotics
	• Antidepressants: SSRIs (DOC) are used in Depression PYQ: FMGE 2023
	• Antipsychotics: certain drugs are approved for unipolar depression
		• Antidepressants: SSRI
		  ○ DOC

Pathogenesis of Psychosis

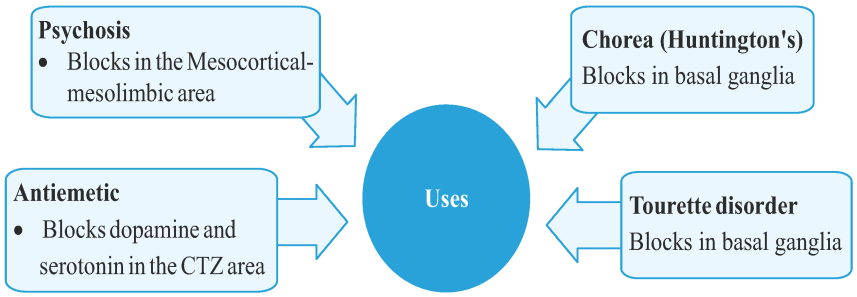
00:05:10

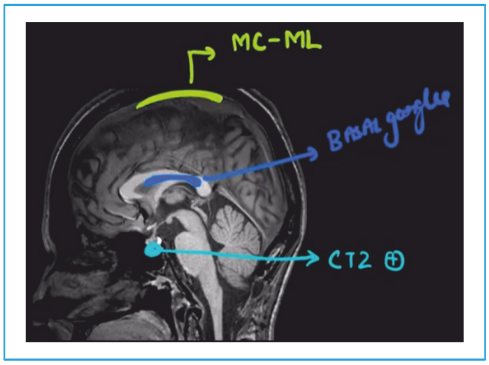
- Psychosis occurs due to excessive amines in the upper part of the brain- Mesocortical- mesolimbic area
- The mechanism of action of antipsychotics is to block amine receptors (Dopamine and serotonin)

Antipsychotic Drugs

00:06:38

- MoA: Block dopamine or serotonin receptor





Classification

	1st Generation: Typical Antipsychotics (Neuroleptic)	2nd Generation: Atypical Antipsychotics
MoA	• Blocks $D_2 > 5HT_2$ receptor	• Blocks $5HT_2 > D_2$ receptor
Effects	• Only reduce positive symptoms of schizophrenia ○ Aggression ○ Hallucination ○ Delusions	• Reduce both positive and negative symptoms ○ Anhedonia ○ Apathy ○ Amnesia ○ Depression
Effectiveness	• Less effective	• More effective
Side effects	• Parkinson's disease- Extrapyramidal symptoms • Prolactinemia	• Metabolic syndrome ○ Increased appetite (Obesity) ○ DM ○ Dyslipidemia
Safe drug	• More dangerous	• Less dangerous • DOC

Treatment of Psychosis

00:14:08

Initial treatment of Psychosis
- Atypical Antipsychotics
  - Ziprasidone
  - Aripiprazole
  - Quetiapine

PYQ: FMGE2021

If resistant till 4 weeks

Change to another atypical antipsychotics

If resistant till 4 weeks

Change to typical antipsychotics

Still resistant

Clozapine: Most effective and Highly dangerous

Typical Antipsychotics

00:16:14

Phenothiazine	-AZINE	• Chlorpromazine • Thioridazine • Mesoridazine • Fluphenazine • Perphenazine • Prochlorperazine	• Least D_2 blocker • Blocks H1: Sedation • Block Muscarinic: Atropine-like effect • Block α blockers: Hypotension • Least risk: Parkinson's disease due to elevated prolactin • Least risk of elevating prolactin levels
Thioxanthenes	-THIX-	• Thiothixene • Flupenthixol • Zuclopenthixol	
Butyrophenone	-RIDOL	• Haloperidol • Droperidol • Benperidol • Penfluridol	• The most potent/specific D_2 blocker • Most effective for psychosis • Maximum risk of Parkinson's disease • Maximum risk of elevating prolactin levels
Misc	---	• Loxapine • Molindone • Pimozide	

One-liners	**Least potent** • Chlorpromazine > Thioridazine
	Most potent • Benperidol > Haloperidol
	Longest (typical AP) • Penfluridol > Pimozide
	Prochlorperazine • Antiemetic used in the treatment of violent vomiting, migraine vomiting
	Thioridazine (RID) • Banned since it causes retinal degeneration
	Droperidol + Fentanyl • Neurolept analgesia
	Droperidol + Fentanyl + N_2O • Neurolept anesthesia

Chlorpromazine

00:24:06

Indications	Side effects
• **DOC:** Intractable Hiccups • Amphetamine poisoning (causes psychosis and H TN) • Allergic pruritus: Antihistaminic action	• Sedation • Cholestatic jaundice • Blue-grey skin • Cornea verticillata (also caused by Amiodarone)

Atypical Antipsychotics

00:26:28

- Based on functional classification

Receptors	How to Identify	Drugs	
Blocks $5HT_{2A} > D_2$ antagonist	Ends with PINE or DONE	• **C**lozapine • **O**lanzapine • **Z**otepine • **A**senapine • **Q**uetiapine • **Z**iprasidone • **R**isperidone • **I**laperidone • **S**ertindone • **P**aliperidone • **L**urasidone	• Max. D_2 block: Risperidone o High risk of Parkinson's disease • Least: Clozapine o Low risk
$D_{1/2}$ Partial Agonist + $5HT_{2A}$ Antagonist	PIPRAZOLE	• Aripiprazole • Brexpiprazole • New drug: Cariprazine	• Aripiprazole is only antipsychotic drug causing vomiting due to low D_2 stimulating property
D_2+ D_3 Antagonist	SULPIRIDE	• Sulpiride • Amisulpride • Levosulpiride	• Increases GI motility (Prokinetic) • Used in the treatment of constipation, GERD
5-HT_{2A} Inverse Agonist	SERIN	• Pimavanserin	• No action on the dopamine receptor • Doesn't produce Parkinson's disease • Approved to treat psychosis in Parkinson's disease

Q. Which antipsychotic does not act on Dopamine (D_2) receptors?

Ans. Pimavanserin

Q. Overall Least risk of Parkinson's and Prolactin elevation?

Ans. Pimavanserin > Clozapine > Aripiprazole or Ziprasidone

Q. Least risk prolactin and Parkinson's among typical antipsychotic

Ans. AZINE: Chlorpromazine > Thioridazine

Q. Maximum risk prolactin and Parkinson's among atypical antipsychotic

Ans.

- Risperidone
- Max: typical
  - Haloperidol

Uses of Antipsychotics

00:36:10

Schizophrenia: All drugs
- Typical AP: Decreased positive symptoms
- Atypical AP: Decreases both positive and negative symptoms
- Asenapine: Decreases negative symptoms
- Lurasidone: Acute attack of decompensated/ fatal psychoses

Bipolar Disorder: Mood stabilizers
- Atypical AP > Typical AP
- Quetiapine: Makes a person quite

Uses of Antipsychotics

Acute Mania
- Atypical AP > Typical AP

Unipolar depression
- Quetiapine
- Aripiprazole
- Amisulpride
- Brexpiprazole

Other uses of Antipsychotics

Drug approved for Autism
- Risperidone
- Aripiprazole (Age < 7 yrs)

Drug approved for Schizoaffective disorder
- Paliperidone: Prodrug
- Active: Risperidone

Risperidone approved for
- Schizophrenia
- Autism
- Bipolar Disorder
- Off label use in Anxiety disorder like OCD and GAD

Route of Administration

00:41:35

Oral
- All drugs
- IM depot with Z technique is given in patients with poor compliance once a month

Intramuscular Depot (Z technique)		
High	Haloperidol	Typical antipsychotics
Five	Fluphenazine	
Zero	Zuclopenthixol	
Price	Perphenazine	
P	Paliperdone	Atypical antipsychotics
A	Aripiprazole	
R	Risperidone	
O	Olanzapine	

Intravenous

- In emergency like Acute Mania
  - Olanzapine
  - Clozapine
  - Ziprasidone
  - Haloperidol

Intranasal

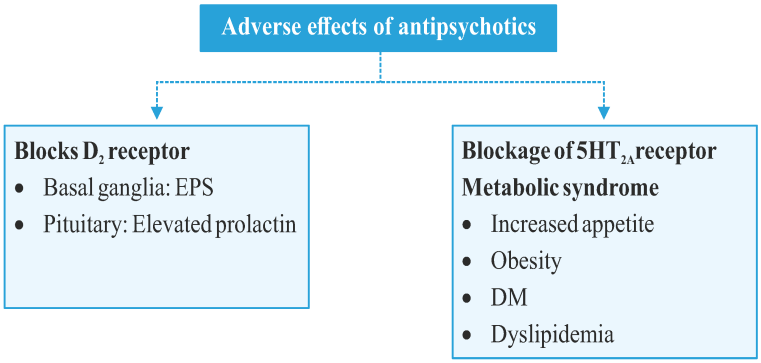
- Loxapine

Sublingual

- Asenapine

Adverse effects of Antipsychotics

00:44:48



Elevated prolactin

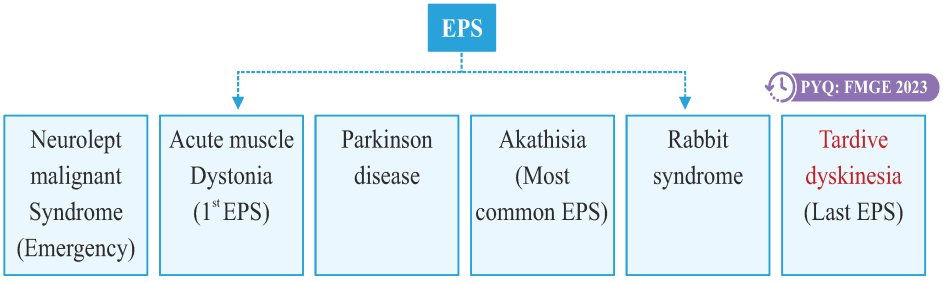
- Galactorrhea
- Amenorrhea
- Infertility
- Max. Risk: Typical AP- Haloperidol
- Atypical AP- Risperidone
- Least risk: Pimavanserin > clozapine

Extrapyramidal Symptoms

00:47:18

Pathophysiology

- Blockage of D_2 receptor in basal ganglia
  - Increased muscle tone
- **Note:** Mnemonic- Never APART



Neurolept Malignant Syndrome

00:49:56

Pathophysiology

Marked rigidity → Hyperthermia → Rhabdo-myolysis (Muscle damage) → Lactic acidosis → Myoglobinuria (Cola color urine)

Diagnosis

- Increased CPK enzyme

Treatment

- Dantrolene (DOC)
  - Muscle relaxant
  - Life-saving drug
  - Acts by blocking SERCA-2 channels/Ryanodine receptor blocker
  - Also DOC for malignant hyperthermia
- Drugs causing malignant hyperthermia (mnemonic- SHAL):
  - → Succinylcholine
  - → Halothane (max. risk)
  - → Atropine
  - → Lignocaine
- Bromocriptine

Apart	Features	Treatment

Acute muscle Dystonia
1st dose (1st EPS)
	• Spasm of head/ neck muscles
	  ○ Torticollis
	  ○ Uprolling eyes (oculogyric crisis)
		• Inj. Anticholinergics
		  ○ Promethazine
		  ○ Diphenhydramine

Parkinsonism
(1 month)
	• Resting tremors
	• Bradykinesia
	• Festinating gait
		• No role of levodopa
		• Oral anticholinergics
		  ○ Benzhexol
		  ○ Benztropine

Akathisia **(Most common EPS)**	**Anxiety like situation** • Restless • Unable to sit quietly • Aggravated by smoking	• Anti anxiety drugs • DOC: Propranolol (C/I in asthma) • Asthma patients: Benzodiazepines (diazepam)

Rabbit Syndrome
(Months)
	• Peri oral tremors	• Oral anticholinergics
		  ○ Benzhexol
		  ○ Promethazine

Tardive Dyskinesia
(Slow abnormal excessive movements)
• Last, Permanent EPS
• The prolonged duration of blockage of D_2 receptors causes super sensitivity and leads to dyskinesia.
	• Oro-facial movements
	• Lip smacking
	• Pouting
	  ○ Females > Males
		• Stop AP drug
		• Start Clozapine
		  ○ Not disappearing
		• Add: Dopamine depleters
		  ○ Valbenazine
		  ○ Tetrabenazine: DOC for Huntington's disease

Clozapine

01:03:30

- The most effective Antipsychotic drug
- DOC for
  - Resistant psychosis
  - Resistant Mania
- Least risk of EPS & prolactinemia d/t less action on D_2 receptor (acts on D_4 receptor)
- The structure of Clozapine is similar to Di-Benzodiazepine, hence it is a sedative drug
- Metabolized by CYP1A2 enzyme

Adverse Effects

Non- Serious	Serious

• **M**etabolic Syndrome
• **O**besity
• **T**ype 2 DM (Rx: Metformin)
• Dyslipidemia (Rx: statins)
• Hypersalivation
  ○ Due to stimulation of ACh, muscarinic receptors
  ○ Wet pillow syndrome
• **S**edation
	• Dose dependent toxicity:
	  ○ Seizures
	  ○ Myocarditis
	• Dose independent toxicity:
	  ○ Agranulocytosis (idiosyncratic reaction)

- Clozapine should be stopped
  - TLC < 3000/mm³
  - Neutrophil < 2000/mm³
    → Agranulocytosis

PYQ: INICET 2023

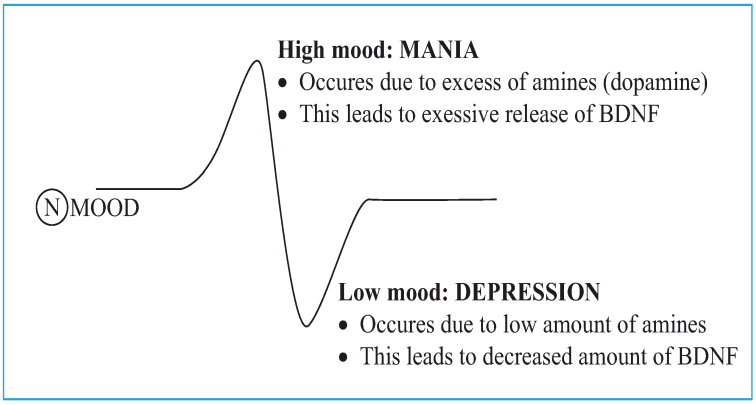
- Avoid combining with Carbamazepine

One Liners	**Max weight gain/obesity/metabolic syndrome** • Olanzapine > Clozapine • Blockage of 5-HT_{2c} stimulates appetite receptor
	Least weight gain • Aripiprazole > Ziprazole
	Weight Loss • Molindone
	Lorcaserin • 5-HT_{2c} Agonist • Anti-obesity drug • Banned due to the risk of causing cancers
	Increase Stroke risk • Risperidone
	Cataract • Clozapine > Quetiapine
	QT Prolongation • Sertindole • Ziprasidone • Quetiapine
	Pregnancy • Max. placenta crossing: Olanzapine (Unsafe) • Least placenta crossing: Quetiapine (Safest)

44 MOOD STABILIZERS

Bipolar disorder

- Also called MDP (Mania Depressive Psychosis)



Treatment

- Mood stabilizers

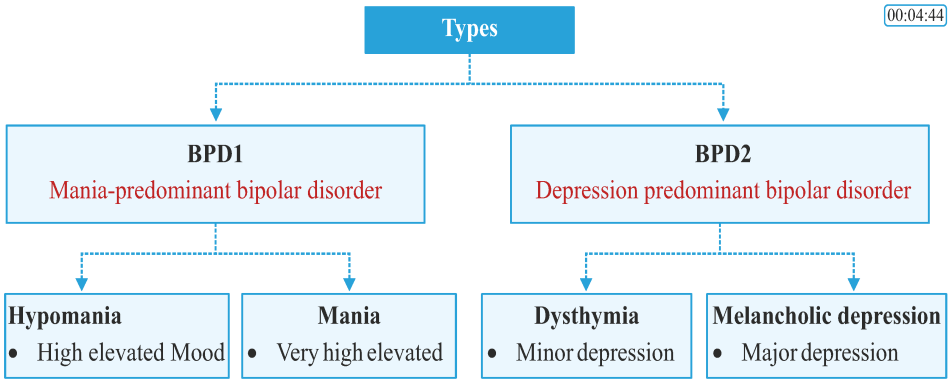
Mood stabilizers	Lithium

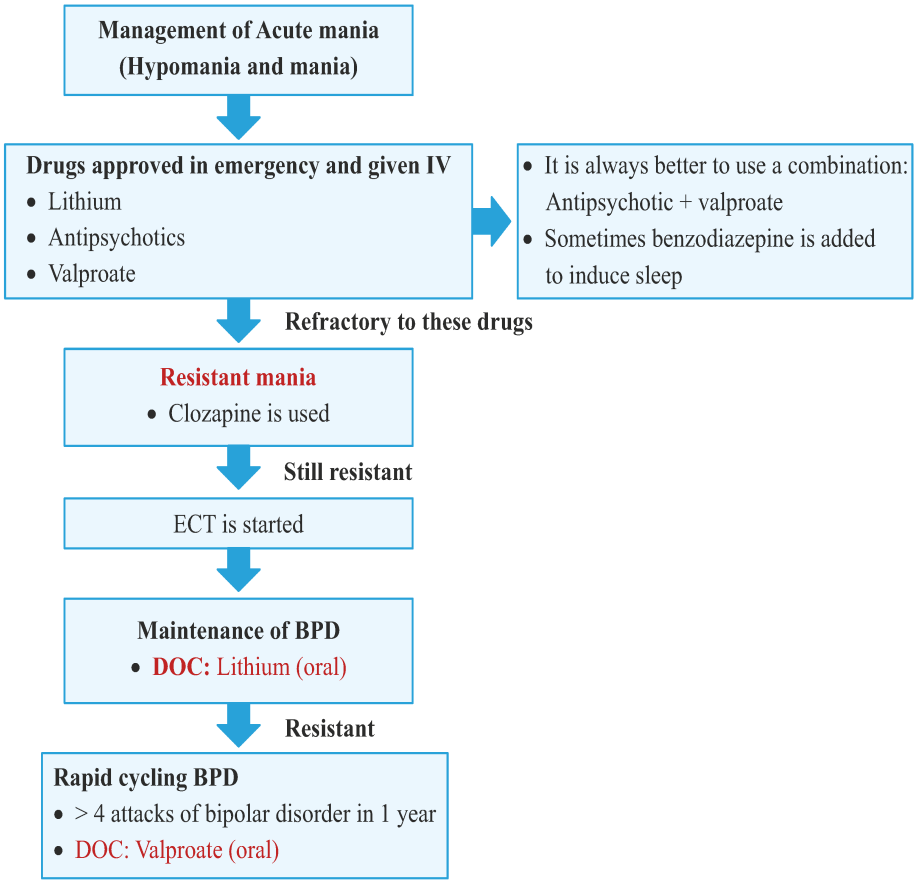
	• Anti-epileptics
	  ○ Valproate/ Divalproex
	  ○ Oxcarbazepine, Eslicarbazepine, Carbamazepine
	  ○ Lamotrigine
	  ○ Topiramate

	Antipsychotics
	Gabapentin
	Off label drugs (not approved yet) • Topiramate • Oxcarbazepine

- **Note: Mnemonic of drugs- Low VOLTAGE**

00:04:44





- **BPD in pregnancy**
  - **Safest drugs:** Antipsychotics
  - Absolute contraindication: Valproate
    → Leads to Folic acid deficiency
    → Risk of neural tube defects

- **Lithium**
  - Not given in emergency or ICU patients
  - Increased risk of seizures
  - Needs continuous monitoring

PYQ: INICET 2023

- **Lamotrigine**
  - Contraindicated in mania predominant BPD
    → Risk of Steven-Johnson syndrome due to high dose requirement.
  - Only given in depression-predominant BPD

Antidepressants in BPD

00:11:54

- Antidepressants → increase amine levels in the brain (do not stabilize mood) → precipitate an attack of mania
- For this reason, they are never given alone and always combined with any mood stabilizer.

Lithium

00:13:35

Uses

- Bipolar disorder
- Hypnic headache (occurs in sleep)
- Anti-suicidal action (another drug is clozapine)
- Resistant cases of depression

MoA

- The poorly understood hypothesis is
  - Increase the level of amine if the mood is low by inhibiting the Glycogen synthase kinase-3 enzyme
  - Decrease the level of amine if mood is high
    → Inhibits inositol monophosphatase enzyme
    → Inhibits the release of amines
    → Stabilizes neuronal membrane

Pharmacokinetics

- Salt: Lithium citrate or carbonate is used
- **RoA:** Oral and IV (as properties are similar to sodium)
- **Half-life:** 24 hours
- **Metabolism:** Not metabolized in the body
- **Excretion:** Excreted unchanged in all body secretions
  - Maximum in urine
  - Sweat, saliva, and breastmilk

Contraindications

- During breastfeeding
- In children <12 years
- Should be stopped **atleast 24 hours before surgery**

Therapeutic index

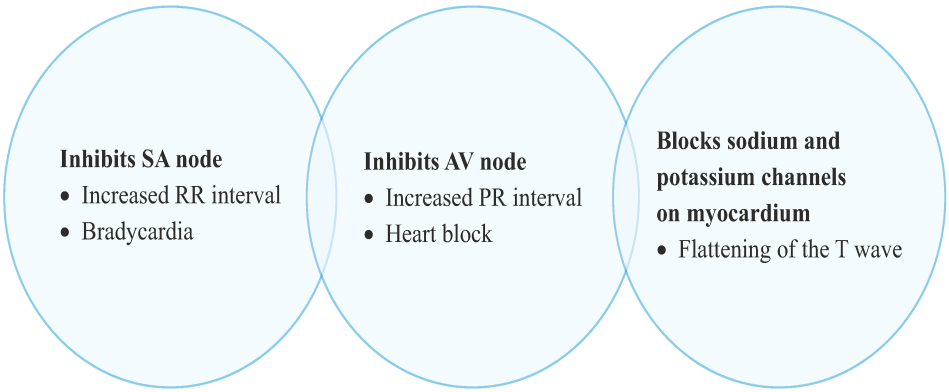
- Narrow therapeutic index drug
- Requires therapeutic drug monitoring (blood samples should be **taken after 12 hours of the last dose of lithium)**

- **Serum Lithium levels**

Levels	Condition
0.6 to 1 mEq/L	For maintenance of BPD
1 to 1.5 mEq/L	For the treatment of acute mania
> 1.5 mEq/L	Produces toxicity
> 2 mEq/L	Hospitalization of the patient is required
> 4 mEq/L	Indication to start hemodialysis to remove lithium from the body

Adverse effects (Mnemonic: LITHIUMS)	**L**eukocytosis (due to this can be given in neutropenia in Felty syndrome)
	Increase in weight and thirst
	Tremors • Normal doses: Fine tremors • Toxic doses: Coarse tremors
	Hypothyroid Goiter • By inhibiting T3 and T4 synthesis • Increased TSH due to no negative feedback
	Increased nausea and vomiting (GIT upset) – The most common side effect
	Urination (excessive) • Due to blockage of ADH receptor in the kidneys • Leads to polyuria – Nephrogenic diabetic insipidus
	Mental changes • Tinnitus • Deafness • Seizures • Ataxia
	Skin changes • Acneiform eruptions • Aggravates psoriasis

- **ECG changes**

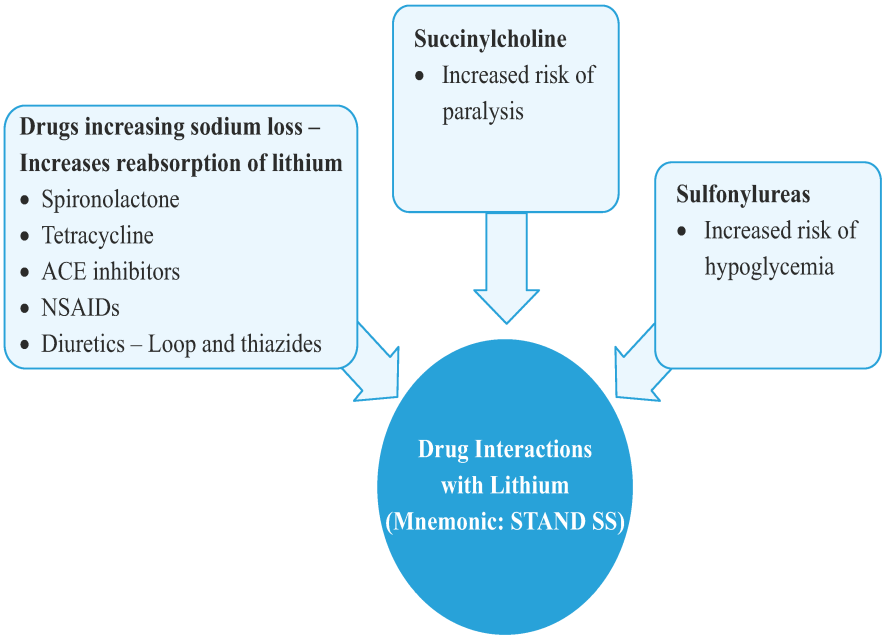


Treatment of Lithium poisoning

00:29:38

- **Hydration**
  - Increases lithium excretion in urine
  - Adding Mannitol helps excretion in urine.
- If lithium produces nephrogenic diabetic insipidus - Amiloride is used

00:31:05



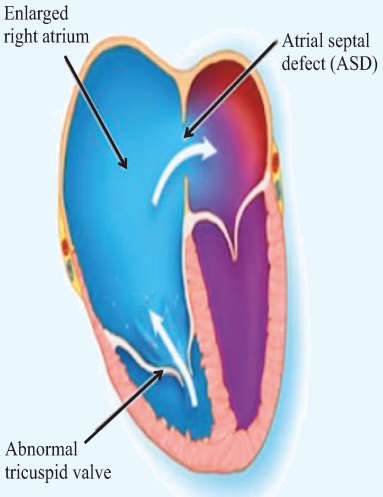
Lithium in pregnancy

00:33:30

- Not safe in pregnancy as it is teratogenic.

Teratogenic effects

- Ebstein anomaly (cardiac malformation in the fetus)
  - The right atria and right ventricle become a single chamber.
  - The pressure of blood in the right heart increases and blood flows from right to left atria.
  - Starts from tricuspid valve abnormality.
  - X-ray: Box-shaped heart
- Floppy infant syndrome: Causes hypotonia.
- Goiter (hypothyroid)



Important Information

- Valproate is the most teratogenic drug.

45 ANTI DEPRESSANT DRUGS

Depression

Depressed mood +

Other symptoms
- Sleep abnormality
- Lack of concentration
- Suicidal tendencies
- Loss of libido
- Worthlessness
- Hopelessness
- Helplessness

- Depression is diagnosed if the symptoms persist for >2 weeks.

Pathophysiology of Depression

- Monoamine hypothesis of depression

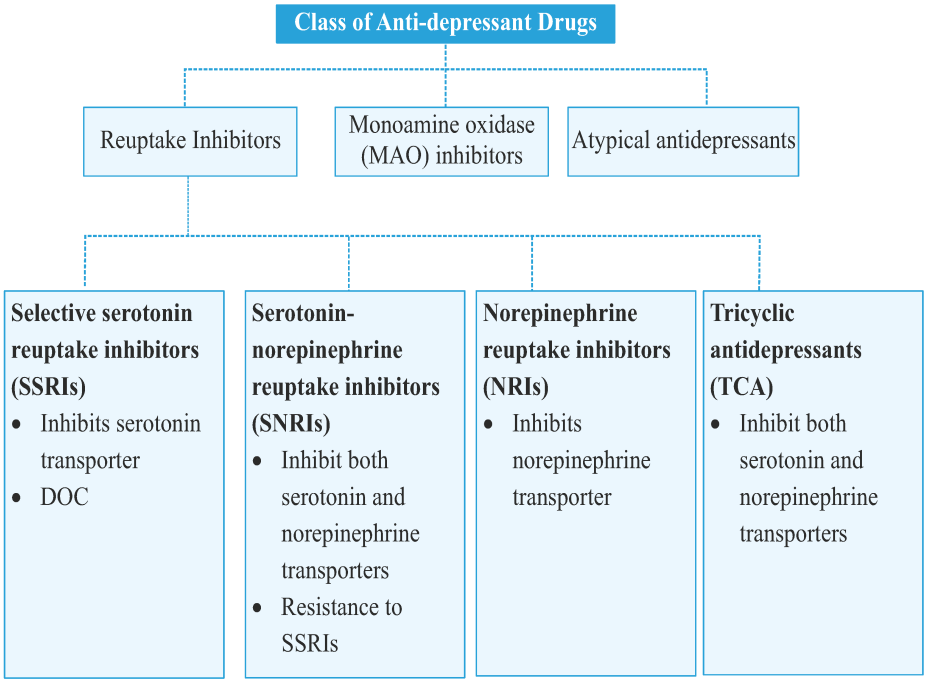
Neurons
↓
Reduced levels of amine (serotonin, norepinephrine) in the raphe nucleus and nucleus accumbens
↓
Changes
↓
Decreased expression of C-fos gene
↓
Decrease the production of Brain-derived neurotrophic factor (BDNF)
↓
Decrease in dendritic and axonal connections
↓
Decrease in neuronal plasticity

- Antidepressants: Increase amine levels in the brain

Neurons
↓
Releases of serotonin or norepinephrine
↓
Reuptake of serotonin or norepinephrine by the same neuron by two different transporter
↓
Degradation of amine by mono-amine oxidase enzyme

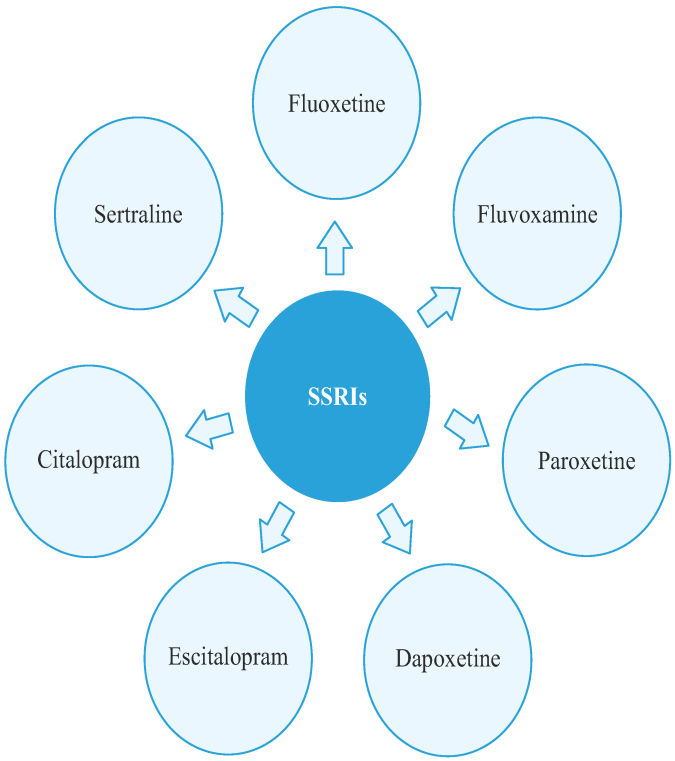
- Transporter of serotonin: Serotonin transporter
- Transporter of norepinephrine: Norepinephrine transporter

00:06:27



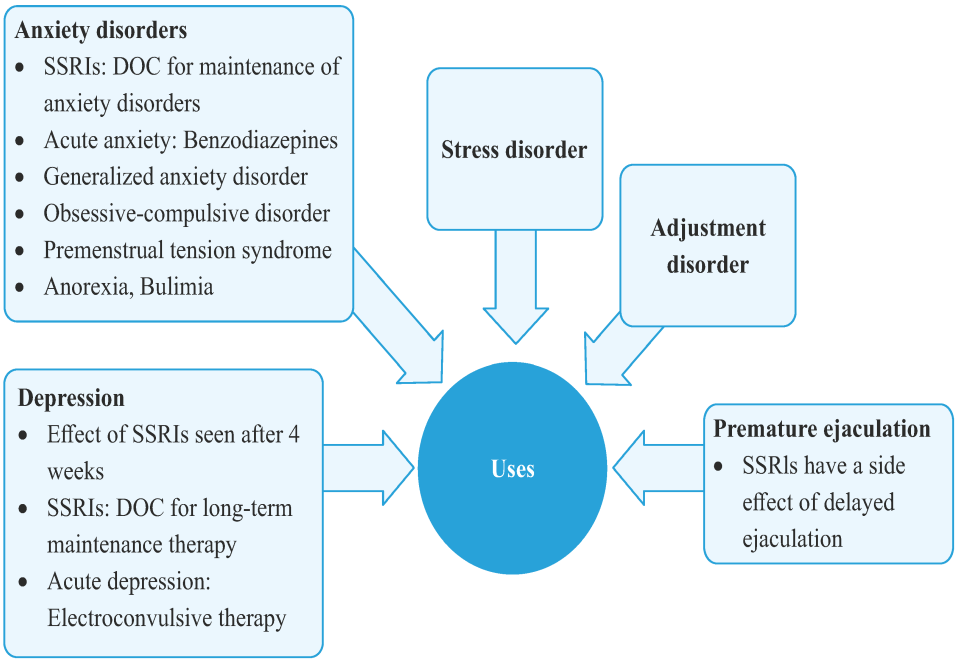
Selective serotonin reuptake inhibitors

00:09:25



- DOC for depression
- Two types of depression
  - Unipolar depression: SSRIs are the DOC
  - Bipolar depression: SSRIs + Mood stabilizers
    → SSRIs given alone elevate the mood more than normal and precipitate mania.

- **Note: Mnemonic- DASAP** 00:12:05



Pharmacokinetics of SSRIs 00:15:10

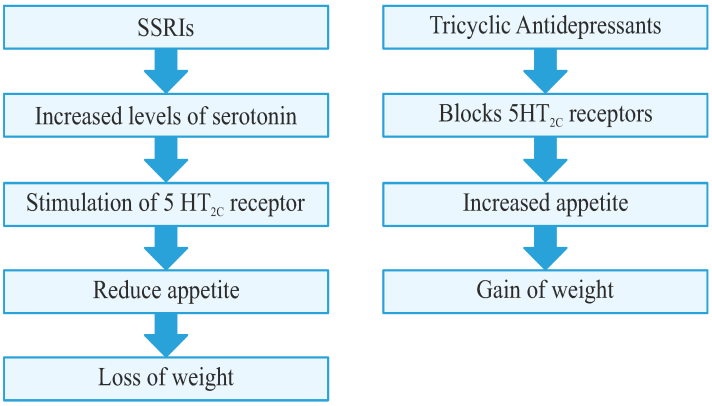
- Metabolism: CYP2D6 enzyme except escitalopram
- Safest SSRI- Escitalopram
  - Has least drug interactions
- Longest acting: Fluoxetine
  - The active drug has a $T_{½}$ of 50 hrs
  - Active form: Norfluoxetine has a $T_{½}$: 200 hrs
- Shortest acting: Paroxetine > Fluvoxamine

Fluoxetine	• Longest acting SSRI • Approved for patients <18 years of age
Fluvoxamine	• Second short-acting drug • Recommended for obsessive-compulsive disorder and generalized anxiety disorder • Not approved for depression
Escitalopram	• Safest SSRI • DOC: Premenstrual tension syndrome ○ Overall DOC: Oral contraceptive pills • Safe in heart disease patients
Sertraline	• Safe in heart disease patients
Paroxetine	• Maximum risk of sexual dysfunction ○ Causes delayed ejaculation • Used to treat Premature ejaculation • The most unsafe drug in pregnancy
Dapoxetine	• Used to treat premature ejaculation

Adverse Effects of SSRIs

00:20:46

Nausea and vomiting	• M/C side effect (Rx: Ondansetron- 5-HT_3 receptor antagonist)
Decreased secretions	• Dry eyes • Dry mouth • SSRIs: Has mild anticholinergic action
Sexual dysfunction	• Characteristic side effect • Delayed ejaculation • Anorgasmia • Loss of libido **Trazodone** PYQ: INICET 2023 • SSRI-like drug and block $5HT_2$ receptor ○ No erectile dysfunction and loss of libido but causes Priapism (extended erection)
Seizures	• Increased risk of seizures due to increased levels of serotonin.
Suicides	• Increases the risk
Severe anxiety	• For initial four weeks: SSRIs + Benzodiazepines • Benzodiazepines: Addictive drugs ○ Not recommended for long-term use
Severe bleeding	• Due to thrombocytopenia
SIADH	• Increased secretions of ADH hormone in brain



New SSRI like Drugs

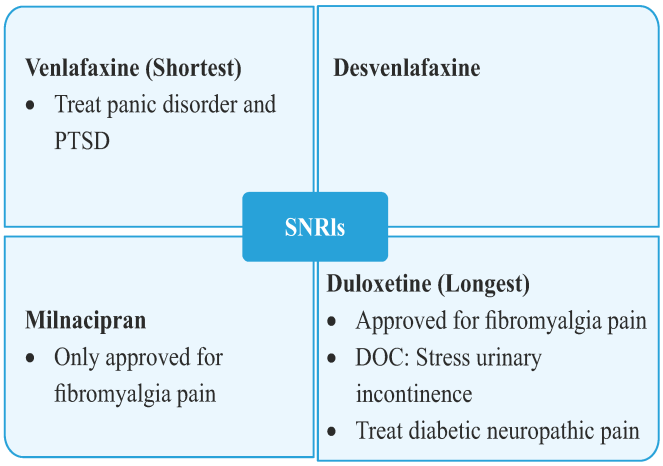
PYQ: INICET 2021

Vilazodone	• Other Name: Serotonin stimulator and modulator • $5HT_{1A}$ receptor agonists • Treatment ○ Depression ○ Anxiety disorders
Vortioxetine	

Selective norepinephrine reputake inhibitors

00:30:40

- **Note: Mnemonic- Very Difficult MD**



- Used in resistant cases of depression to SSRIs

Side effects

- Same like SSRIs
- Also produce Hypertension: Increase in norepinephrine levels (Vasoconstriction)
  → Causes diastolic hypertension

Norepinephrine Reuptake Inhibitors

00:35:08

- Drug: **Atomoxetine**
- Used in ADHD associated with Tourette syndrome
- But in ADHD, DOC is Methylphenidate
- Methylphenidate increases the side effects of Tourette syndrome

SSRIs and SNRIs in Pregnancy

- All SNRIs + Paroxetine: Unsafe in pregnancy
- Fetus: Persistent pulmonary hypertension
  - Maximum seen when used in 3rd trimester

Drugs discontinuation Syndrome

- Seen in sudden stoppage of antidepressants
- Rebound increase in
  - Insomnia
  - Anxiety
  - Suicidal tendency
- **Maximum with shortest acting antidepressants**
  - Paroxetine
  - Venlafaxine

PYQ: FMGE 2021

- **Minimum with longest acting antidepressants**
  - Fluoxetine

Tricyclic Antidepressants (TCA)

00:41:50

- Less commonly used
- Inhibit reuptake of serotonin and norepinephrine
- Non selective: Acts on many unwanted receptors
- Have three cyclic rings

Inhibition of norepinephrine is equal to serotonin reuptake	**Mnemonic: ICT DAD** • Imipramine- Active form: Des-imipramine • Clomipramine • Trimipramine • Doxepin • Amitriptyline- Active form: Nortriptyline • Dothiepin

Inhibition of norepinephrine >>> serotonin reuptake	**Mnemonic: Recombinant DNA**
	• **R**eboxetine
	• **D**es-imipramine
	• **N**ortriptyline
	• **A**moxapine
	  ○ Potent dopamine blocker
	  ○ Causes drug induced Parkinson's disease
	  ○ Increases the levels of prolactin

Bicyclic antidepressants	• Has two fused rings ○ Viloxazone

Tetracyclic antidepressants	• Has four fused rings
	• **Mnemonic: MAM**
	  ○ **M**irtazapine PYQ: AIIMS2020
	  ○ **A**moxapine
	  ○ **M**ianserin

Uses of TCA

00:46:47

- **Mnemonic**: **DENi MCD**

Depression	• DOC: SSRIs

Enuresis	• Other Name: Bedwetting in children
	• DOC: Desmopresin
	• Others
	  ○ Oxybutynin: Anticholinergic drug
	  ○ Imipramine: Nocturnal enuresis

Neuropathic pain	• DOC: Pregabalin
Migraine prevention	• DOC: Propranolol
Clomipramine	• Used in Obsessive compulsive disorder

Doxepin	• Classified as
	  ○ Tricyclic antidepressant
	  ○ Antihistamine drug
	• Used in Pruritus, itching

Adverse effects of TCA 00:49:25

Mechanism	Effect
Increase serotonin in brain	• Seizures (Side effects of all antidepressants)
Blockage of histamine receptor	• Sedation
α blockage	• Postural hypotension
Muscarinic blockage	• Effect of Atropine poisoning → Hyperthermia, dry eyes/mouth, constipation, urinary retention, mydriasis • Imipramine is used to treat nocturnal enuresis • TCA's are contraindicated in Glaucoma
Sodium blockage	• Local anesthetic effects and decreases nerve conduction ○ Used in treatment of Neuropathic pain
Potassium blockage	• QT prolongation → Arrhythmia
Serotonin blockage	• Weight gain

Properties of TCA

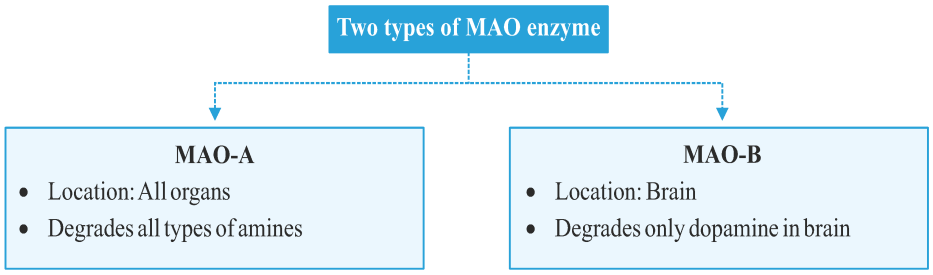
- Narrow therapeutic index drugs
- Requires continuous monitoring: Therapeutic drug monitoring
- SSRIs: No monitoring is required

TCA poisoning

- Sodium bicarbonate (Hypertonic sodium bicarbonate) is the antidote as it protects the heart in case of QT prolongation, Arrhythmia.
- If arrhythmias are resistant to treatment, Lignocaine is added.
- For Atropine like side effects: Add physostigmine.

Monoamine Oxidase Inhibitors

00:57:35



- MAO-A and MAO-B are mitochondrial enzymes.
- Amines
  - Catecholamines: Epinephrine, norepinephrine, dopamine
  - Serotonin
  - Histamine

Non selective MAO inhibitors	• Highly dangerous drug interactions
	• Irreversible inhibitors of MAO-A & MAO-B enzymes
	  ○ Other Name: Hit and Run drug, suicide inhibitor
	• **Mnemonic: PINT**
	  ○ **P**henelzine
	  ○ **I**socarboxazid
	  ○ **N**ialamide
	  ○ **T**ranylcypromine

Reversible inhibitors of MAO-A	• Inhibits MAO-A enzyme
	• Reversible inhibitors
	• Safer drugs
	• **Mnemonic: CM**
	  ○ Clorygiline
	  ○ Moclobemide
	• Treat: Depression, phobias
	• Safe in heart disease patients

Selective MAO-B Inhibitors	• Inhibits MAO-B enzyme
	• **Mnemonic: SR**
	  ○ Selegiline: Available as transdermal patches for treatment of depression
	  ○ Rasagiline
	• Treat depression, Parkinson's disease

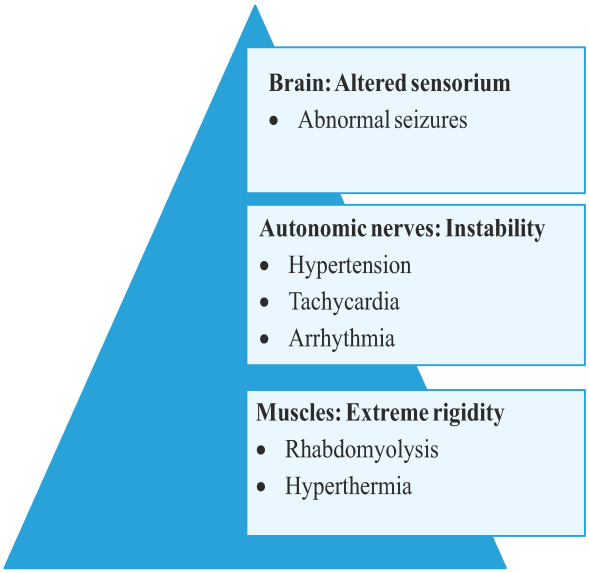
Drug interactions of MAO Inhibitors 01:05:05

Mechanism	**Effect**
Degradation of Tyramine	• Tyramine is degraded by MAO-A enzyme and administering MAO inhibitors increases the levels of Tyramine leading to Hypertensive crisis or Cheese reaction
Degradtion of Levodopa	• Hypotension
Degradtion of Ephedrine	• Hypertensive crisis
Degradtion of Tramadol	• Increase the level of serotonin in brain leading to Serotonin syndrome.
MAO Inhibitors are never combined with reuptake inhibitors (SSRI, SNRI, Fluoxetine)	• Increase the level of serotonin in the brain leading to Serotonin syndrome
Linezolid (Antibiotic)	• Inhibits MAO enzyme and causes Serotonin syndrome

Washout period

- MAO I + SNRI: Gap 1 week
- MAO I + SSRI: Gap 2 weeks
- MAO I + Fluoxetine: Gap 5 weeks

Serotonin Syndrome 01:09:47



Treatment

- Anti serotonin drugs- DOC: Cyproheptadine
- **Other drugs**
  - Ketanserin
  - Olanzapine: Antipsychotic drug
- Extreme rigidity: Dantrolene (Muscle relaxant)

Atypical Antidepressants 01:12:46

Bupropion	• **Mechanism:** Norepinephrine dopamine reuptake inhibitor
	• Use
	  ○ Anti-smoking drug
	  ○ Anti-obesity drug
	• Side effects: Seizures (Maximum)

Trazodone	• **Other Name:** Serotonin antagonist and reuptake inhibitor
	  ○ Has serotonin blocking property
	  ○ $5HT_2$, $5HT_3$ antagonist
	  ○ Has SSRI activity
	• Advantage:
	  ○ Doesn't produce nausea and vomiting- antiemetic effect
	  ○ No sexual dysfunction: $5HT_2$ blockage
	• Side effect: Priapism- Prolonged penile erection
	• Nefazadone: Hepatotoxic (banned for use)

Mirtazapine and mianserin	• Noradrenaline and selective serotonin antagonist
	  ○ Blocks α_2 receptor of noradrenaline
	  ○ Blocks $5HT_2$, $5HT_3$ receptors
	• Produces sedation
	• DOC for Depression with Insomnia
	• Also have antiemetic effect

Buspirone and gepirone	• $5HT_{1A}$ receptor partial agonist • Treatment of generalized anxiety disorder
Amineptine	• Norepinephrine dopamine reuptake inhibitor • Increase the release of dopamine • Treat: Depression
Tianeptine	• Other Name: Serotonin reuptake enhancer • MoA: Acts on opioid receptors and stimulates them • Treat: Depression

1 DIABETES MELLITUS :INSULIN

Diabetes Mellitus

00:00:10

- Metabolic disorder
- Increased catabolism in the body because of insulin defect
  - Decrease in insulin (Anabolic hormone)

Pathogenesis

- Glycogen breakdown from liver: produce hyperglycemia and glycosuria
- Adipose tissue: produce lipolysis, hyperglycemia, glycosuria and ketogenesis
- Protein breakdown from muscle: produce hyperglycemia and glycosuria
- Ketone formation due to lipolysis
- Metformin: Inhibit gluconeogenesis
- Pioglitazone: Inhibits lipolysis

Diagnosis of DM

00:04:00

Diagnosis of DM	Fasting blood glucose	Post prandial blood glucose	HbA1c
Normal	<100 mg/dl	<140 mg/dl	<5.6%
Pre diabetes (IGT)	100-125	140-200	5.6-6.5
Diabetes mellitus	>126 mg/dl	>200 mg/dl	>6.5%

- Diabetes mellitus- Start drugs
- Pre diabetes- Lifestyle modification

Drugs for Diabetes

00:07:08

1. Insulin- Most important
2. OHA- Oral hypoglycemic agents or AHA- Anti hyperglycemic agents
3. Treat complications

Types of Diabetes

00:08:59

- Depends on the defect of insulin

Type 1 DM	• Less common • Absolute insulin deficiency • Autoimmune disease- Antibodies destroy β cells of pancreas • DOC- Insulin ○ Add on drugs to insulin- Acarbose, pramlintide- (OHA Drugs)

Type II DM	• Most common
	• Relative insulin deficiency
	  ○ Cells doesn't respond to insulin but insulin is present
	  → Peripheral resistance to insulin
	• Seen in obesity, sedentary lifestyle: Metabolic syndrome

	• **DOC:** Metformin (OHA) ↓ Add other OHA ↓ Insulin • All drugs are recommended
Gestational DM	• Occurs during pregnancy • DOC: Insulin injections ○ Metformin ○ Glyburide (Glibenclamide)

Insulin

00:14:25

- 1st hormone to be discovered
- Synthesized by Banting and Best in year 1921
- Secreted from the β cells of pancreas
- Endocrine portion of pancreas
  - α cells: Secrete glucagon hormone
  - β cells: Secrete insulin + C peptide + Amylin hormone
  - δ cells: Secrete an inhibitory hormone somatostatin

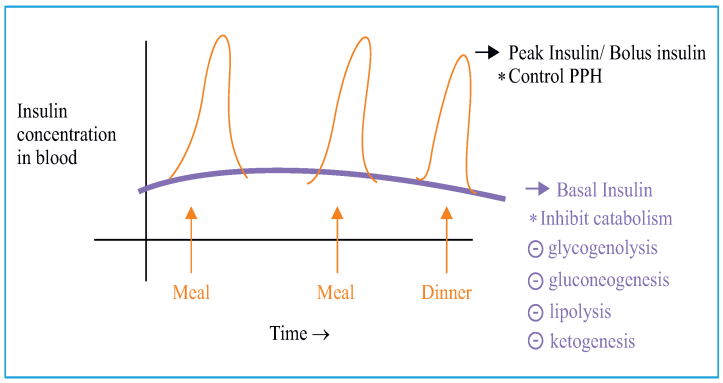
Synthesis

Pre-Pro-insulin from RNA
↓
Proinsulin
↓
Insulin + C peptide
↓
Together released into blood from pancreas

- Importance of C peptide
  - Marker for insulinoma
  - Differentiate type 1 from type 2
  - Endogenous vs exogenous insulin
- Exogenous insulin- Doesn't contain C peptide

Pattern of Insulin Secretion

00:18:21



- Time vs insulin concentration graph
  - X axis: Time
  - Y axis: Insulin concentration in blood
- Peak insulin- After meals
  - Other Name- Bolus insulin
  - Control postprandial hyperglycemia
- Basal insulin: Inhibits catabolism
  - Inhibits glycogenolysis in liver
  - Inhibits gluconeogenesis
  - Inhibits lipolysis and ketone formation
- Type1 DM: More risk of ketone formation
- Degradation of insulin by: Insulinase enzyme - Produced by kidney

Important Information

- Insulin requires dose reduction in renal failure patients

- ROA: Injection
  - Insulin is a peptide hormone, hence cannot be given orally

Injectable Insulin

00:22:46

Types of insulin	Duration of action	Name of insulin	Properties
Ultrashort (Rapid) acting insulin	3hrs	L: Lispro (Shortest) A: Aspart G: Glulisine	• Monomeric insulin ○ All the molecules of insulin are separated • Rapid onset of action
Short acting insulin	6hrs	Regular insulin	• Insulin attached to zinc • Other Name: Hexameric zinc insulin • Addition of zinc- Longer action of insulin

Intermediate acting insulin	12-18 hrs	Lente	• Mixture of
			  ○ Semilente or amorphous insulin (Short acting- 30%)
			  ○ Ultra lente or crystalline insulin (Long acting- 70%)

	15 hrs	NPH: Neutral Protamine Hagedorn	• Insulin is attached to protamine: Longer acting
Long-acting insulin	18 hrs 24hrs	Detemir Glargine (Lantus)	• Attached with a fatty molecule
Ultralong acting insulin	42 hrs	Degludec (Longest acting)	• Attached with a fatty molecule

- Diabetic patients: Combination of 2 insulin
  - Bolus insulin: Control PPH
    - → Taken before meals
    - → Ultrashort acting insulin
      - L: Lispro (Shortest)
      - A: Aspart
      - G: Glulisine
    - → Short acting insulin- Regular insulin
  - Basal insulin: Inhibits catabolism
    - → Can be given anytime
    - → NPH insulin: BD
    - → Glargine: OD
    - → Degludec: Once in 2 days
- NPH is combined with regular or ultrashort acting insulin: Single subcutaneous injection
  - Have same neutral pH

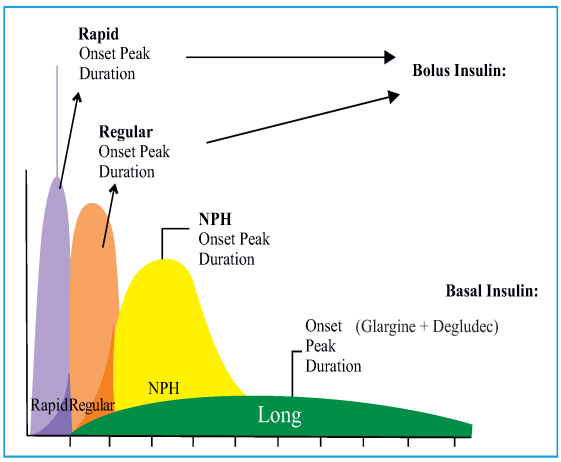
Important Information

- Glargine and Degludec are never combined with any other insulins

- **Mixtard insulin** 00:36:16
  - Mixture of two insulins
  - Lispro: NPH or Regular: NPH
  - Ratio - 30:70 or 50:50
  - ROA: Subcutaneous injection
  - Have the same neutral pH (7.4)

- **Glargine and Degludec**: Given as separate injections
  - With Lispro or regular insulin
  - Bolus or basal insulin
  - Other Name: Basal-Bolus regimen
    - → Better glycemic control
  - Glargine: Acidic insulin (pH 4)

Graph Image- Insulin Action 00:40:05



- Rapid and regular insulin: Bolus insulin
- NPH + Glargine + Degludec: Basal insulin
- Peak less insulin- Glargine + Degludec
  - Least risk of hypoglycemia

Preparation of Insulin

00:42:15

01. Animal Insulin

- Beef insulin: Different in 3 amino acids from human insulin
- Pork insulin: Different in 1 amino acids from human insulin
- These are regular, NPH, Lente insulins
  → Increase in allergic reaction
- **Advantage:** Very cheap

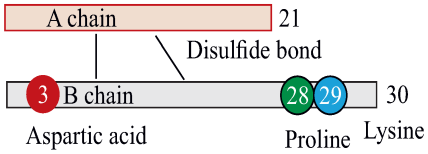
02. Recombinant DNA Technology

Insulin gene
↓
Inoculated into E. coli or yeast
↓
Formation of insulin like peptides

- All insulins can be prepared by this method
- Advantage: Less risk for allergic reactions
- Disadvantage: Very costly

Structure of Human Insulin

00:45:10



- Polypeptide hormone
- Contain 51 amino acids
- Insulin contain two chains
  - A chain: 21 amino acids
  - B chain: 30 amino acids
- Two chains are linked together by disulphide bonds
- 3rd position β chain has aspartic acid
  - 28th position: Proline
  - 29th position: Lysine

Lispro insulin	• Proline is replaced with lysine in β chain
	  ○ 28th position: Lysine
	  ○ 29thposition: Proline

Glulisine	• B 3rd position: Lysine • B 29th position: Glutamic acid
Aspart insulin	• B 28th position: Aspartate
Regular insulin	• No change in amino acid sequence • Other Name: Human physiological insulin

Uses of Insulin

00:48:45

- Type 1 DM (DOC)
- Type 2 DM (+ OHA)
- Patient will take subcutaneous injections in both the cases
  - Insulin- Syringes, prefilled pins
  - Poor compliance then start with Insulin pumps

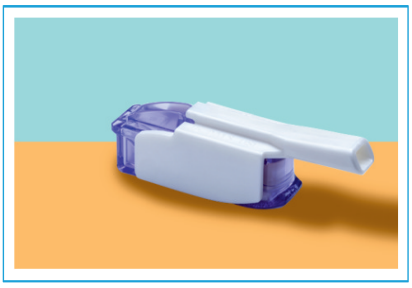
- **Insulin pumps**
- A battery-operated device containing insulin injection
  - A needle is attached to the subcutaneous site
  - The device is kept in the pocket with the syringe attached to the abdomen
  - Has to be changed once every 7-10 months
  - Other Name: Continuous subcutaneous insulin infusion

Acute complications of Diabetes

- Diabetic ketoacidosis: Type 1 DM
- Hyperosmolar hyperglycemic state: Type 2 DM
  - Severe dehydration
  - In this conditions IV insulin is preferred
    → IV Regular insulin
- Hyperkalemia: Regular insulin IV + 50% dextrose
  - Shifts potassium into tissues

Nasal Insulin (Inhaler)

00:53:50



- Other Name-: Afrezza
- Insulin is inhaled as dry powder form
- Shortest acting insulin
  - Shorter than Lispro
- Use: Taken as bolus insulin (Before meals)
  - Control postprandial hyperglycemia (PPH)
- Combined with long acting basal insulin
- Side effects
  - Asthma
  - Lung cancer
- Contraindication: Smokers

Adverse effects of Insulin

00:56:32

- Hypoglycemia (M/C)
  - Dose related toxicity
  - Treatment: Oral or IV glucose
    → Emergency: Intranasal or intramuscular glucagon hormone

- Weight gain
- Hypokalemia
- Lipodystrophy

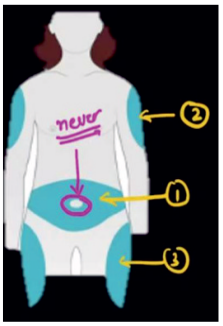
Lipodystrophy

  - Abnormal growth of fat
  - Repetitive subcutaneous injection of insulin at same site
    → Advice to patients: Regularly change the site of insulin injections

Site of Subcutaneous Insulin Injections

00:59:42

- Have four site
  1. Abdomen: Most common
     → Best S/C bioavailability
     → 2 cm around umbilicus: Not given (unpredictable absorption of insulin)
  2. Arm: Upper part
  3. Lateral part of thigh
  4. Buttocks



Treatment of Hyperkalemia

01:01:24

- Serum K^+: >5.5 mEq/L
- ECG: Tall T waves

Excess potassium
↓
Reaches heart
↓
Cardiac arrhythmia or arrest

- 1st protect heart: IV calcium gluconate
  - Inhibits the K^+ entry to heart
- Redistribute K^+ into muscle and fats: IV Regular insulin + 50% dextrose
  - Salbutamol
  - Epinephrine
    → Releases endogenous insulin

- Excrete in urine: Loop diuretics (Furosemide)
- Reduce GIT absorption: Potassium binders
  - Polystyrene
  - Patiromer
  - Sorbitol
- Best and most effective: Hemodialysis

2 DIABETES MELLITUS : ORAL HYPOGLYCEMIC AGENTS

Oral Hypoglycemic Agents (OHA)

- Drugs used in diabetes mellitus except insulin
- All are not oral hence can be called Anti Hyperglycemic Agents (AHA)

Acting at Pancreas

Mnemonic: Smart MAID

- Sulfonylureas, Meglitinides } Insulin secretagogue ↑ insulin secretion
- Amylin analogues
  - Decrease Glucagon
  - Reduces appetite
- Incretins (GLP 1 analogue), DPP-4 inhibitors
  - Increase insulin
  - Decrease Glucagon
  - Reduces appetite

Acting at Peripheral Organs-

Mnemonic: BATS

- Biguanides (Metformin): Acts on liver
- α glucosidase inhibitors (Acarbose): Acts on intestine
- Thiazolidinediones (Piaglitazone): Acts on adipose tissue
- SGLT-2 inhibitors (Gliflozin): Acts on kidneys or nephrons

Drugs Acting at Pancreas

01. Insulin Secretagogues

00:04:16

- **Drugs**
  - Sulfonylureas
  - Meglitinides
- Increase insulin secretion from β cells of pancreas

β cell of pancreas

↓

On the surface it contains ATP sensitive potassium channel

↓

Potassium moves out of the cell through the channel - Normal action

↓

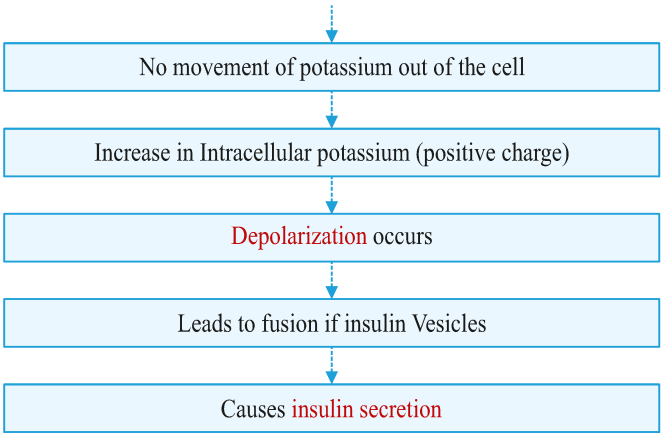
Sulfonylureas block the channel at SUR site

↓

Meglitinides block the channel at KIR 6.1 site

↓

Close ATP sensitive K^+ channel on β cells of pancreas



- Has little minor extra pancreatic action
  - Reduce resistance of insulin on Peripheral organs

Sulfonylureas

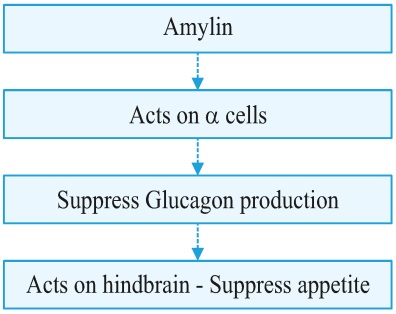
- **2 types**
  - **1st generation** (older drugs) - Ends with amide
    - → Chlorpropamide (least potent)
    - → Acetohexamide
    - → Tolzolamide
    - → Tolbutamide (Shortest acting)
  - **2nd generation** (Newer drugs) - Starts with gli
    - → Glimepiride (most potent) PYQ: FMGE 2021
    - → Glipizide
    - → Gliclazide
    - → Glibenclamide (Glyburide) - Safest drug in pregnancy
- **1st gen drugs**
  - Less potent (more dose required)
  - Long acting drugs except tolbutamide
    - → Release insulin for longer duration
    - → Provides basal and bolus insulin
  - Has higher risk of causing hypoglycemia
- **2nd gen drugs**
  - Most potent (least dose required)
  - Short acting drugs
    - → Release insulin for shorter duration
    - → Cause sudden insulin release for shorter duration
    - → Given before meals to control PPH
    - → Provides bolus insulin
  - Less risk of causing hypoglycemia
- **ROA:** Oral
- Produce weight gain
- Risk of hypoglycemia present
- **Side effects**
  - Sulfonamide derivative - can cause Sulfa allergy (causes bone marrow suppression)
  - Contraindicated in hepatic and renal disease

- Chlorpropamide: 4 side effects (CADS)
  - Cholestatic jaundice
  - Aplastic anemia
  - Disulfiram like reaction (avoided in alcoholics)
  - Syndrome of inappropriate ADH secretion (SIADH)
    - → Increases ADH secretion
    - → Blood water level increases
    - → Fall in blood osmolarity
    - → Causes dilutional hyponatremia
  - Also can be given in treatment of diabetes insipidus
- **Uses:** Type 2 diabetes mellitus

Note
- Sulfonylurea is not effective in type 1 DM because
  - β cell destruction occurs in type 1 DM
  - No insulin secretion
- Also not effective in pancreatectomy

Meglitinides
- **Drugs**
  - Nateglinide (short acting)
  - Repaglinide (long acting)
- **MOA:** Same like sulfonylureas- Close ATP sensitive K^+ channel on β cells of pancreas
- Use: Type 2 DM
- **ROA:** Oral
- Causes weight gain
- Produce hypoglycemia
- Even shorter acting than sulfonylureas
  - Less duration of insulin produced
  - Provide bolus insulin
  - Controls PPH
  - Given before meals
  - Lesser risk of hypoglycemia than sulfonylureas
- **Side effect:** Flu like symptoms

02. Amylin Analogues
- Pramlintide (synthetic form of amylin)
- **Amylin:** Secreted from β cells of pancreas



- **Uses**
  - Given in both type 1 and type 2 DM
  - Add on drug to insulin

- Never combined with insulin in same syringe (pH differences)
- **ROA:** Subcutaneous injection
- Causes weight loss
- No risk of hypoglycemia
- **Side effects**
  - Anorexia
  - Slow down the motility of stomach (gastroparesis)

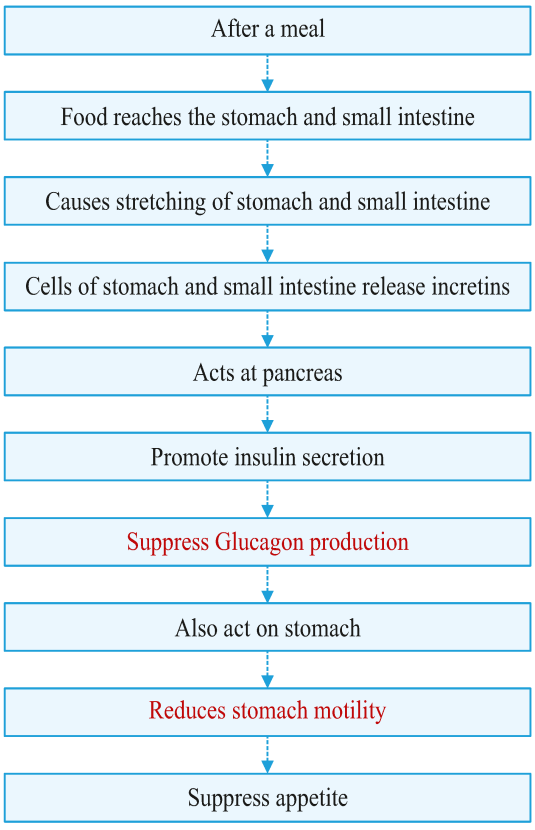
Important Information

Drugs producing hypoglycemia in diabetes

- Insulin
- Insulin secretagogue
  - Sulfonylureas (- Amide or Gli -)
  - Meglitinides (- Glinide)

03. Incretins

- Increase insulin secretion
- Also Suppress
  - Glucagon production
  - Appetite



- **Chemicals in incretin**
  - **GLP** (Glucagon like peptide)
    → GLP-1
    → GLP-2
  - **GIP** (Glucose dependent insulinotropic peptide)

- **Drugs**
  - GLP-1 analogues (end with -natide or -glutide)
    → Used for treatment of type 2 DM
  - Dual GLP-1 + GIP analogue: Tirzepatide
    → New drug
    → Approved for type 2 DM treatment
  - **GLP-2 analogue**
    → Causes growth of intestinal cells
    → Increases absorptive power of intestine
    → Drug: Teduglutide
    → Approved for short bowel syndrome treatment
- Enzyme for degradation of Incretins: DPP-4 (Dipeptidyl peptidase)
- DPP-4 blockers or inhibitors (end with gliptin) - Increases incretin levels

GLP-1 Analogues

- **Drugs (End with:- natide or - glutide)** PYQ: FMGE 2019
  - **Exenatide**
    → 1st drug
    → Obtained from saliva of Gila lizard
    → Also called exendin
    → Shortest acting
  - **Lixisenatide**
    → Albumin bound GLP-1
    → Longer acting
    → Given once a day
  - **Albiglutide** (same as Lixisenatide)
  - **Dulaglutide:** Antibody bound GLP-1
  - **Liraglutide** PYQ: INICET 2021
  - **Semaglutide:** Longest acting drug
- **ROA:** Subcutaneous injection

Important Information
Semaglutide is the only GLP-1 that is given orally

- Causes weight loss
- Liraglutide and Semaglutide: Also approved as anti obesity drug
- No risk of hypoglycemia
- **Side effects**
  - MC: Nausea and vomiting
  - Produce gallstones
  - Pancreatitis
  - Increase the risk of Pancreatic and thyroid cancer (medullary carcinoma of thyroid)
    → Risk is increased in MEN syndrome hence contraindicated

04. DPP-4 inhibitors

- Increase endogenous incretin levels

- **Drugs** (-gliptin)
  - **Saxagliptin**
    - → Only drug metabolized by CYP3A4
    - → Has more drug interactions
  - **Vildagliptin:** Hepatotoxic
  - Alogliptin
  - Sitagliptin PYQ: INICET 2023
  - **Linagliptin:** Safe in renal failure
- **New drug:** Teneligliptin (safe in renal failure)
- **ROA:** Oral
- Maintains neural weight
- No risk of hypoglycemia
- **Side effect**
  - MC: Nausea and vomiting
  - Pancreatitis (lesser than GLP-1)
  - Increase the risk of pancreatic and thyroid cancer (lesser than GLP-1)
  - Increase inflammation in body
    - → DPP-4 enzyme present on lymphocytes
    - → Normally degrades IL and cytokine
    - → DPP-4 inhibitors increase IL and cytokines levels
    - → Causes inflammation
    - → Manifests as
      - – Arthritis
      - – Nasopharyngitis

Drugs Acting at Peripheral Organs 00:47:18

01. Biguanides

- **Drugs**
  - Metformin
  - Phenformin (banned because of deaths due to lactic acidosis) PYQ: FMGE 2020

MOA

Metformin acts on Liver
↓
Metformin stimulates AMPK enzyme in presence of insulin
↓
Inhibits hepatic gluconeogenesis

- **AMPK enzyme**
  - Normally insulin inhibits hepatic gluconeogenesis
  - In Type 2 DM
    - → Peripheral organs do not respond to insulin
    - → Leads to insulin resistance on liver
    - → Hepatic gluconeogenesis continues
      - – Lactic acid and amino acid converts to glucose
      - – More glucose in blood
    - → Metformin inhibits glucose formation
      - – Reduces peripheral resistance to insulin
    - → Leads to increase in blood lactic acid (main side effect)

- **ROA:** Oral
- Mild weight loss

Note
- Metformin Causes
  - Weight loss in obese patients as in type 2 DM
  - Weight neutral in thin patients

- No risk of hypoglycemia

Uses of Metformin
- DOC:
  - Type 2 DM
  - Prediabetes or impaired glucose tolerance
  - Diabetes due to insulin resistance
    - → Seen in females suffering from PCOD
    - → Clozapine induced DM
    - → Cushing syndrome
- **Additional benefits**
  - Reduces lipid levels (Triglycerides)
  - Decreases micro + macrovascular complications of DM
    - → Micro: Diabetic neuropathy, nephropathy, retinopathy
    - → Macro: MI and stroke
- Anti-aging drug
- Dose: 500 mg OD
  - Max up to: 2550 mg/day
    - → Beyond: Increased risk of lactic acidosis

Side effects of Metformin
- Nausea/Vomiting/Diarrhea
- Megaloblastic anemia
  - Reduces vit B12 absorption from GIT
- Lactic acidosis: Dangerous side effects
  - Anaerobic respiration produces lactic acid
  - Hypoxia - Increases production of lactic acid
  - Hypoxia occurs in COPD, CHF, dehydration and sepsis - Avoid metformin

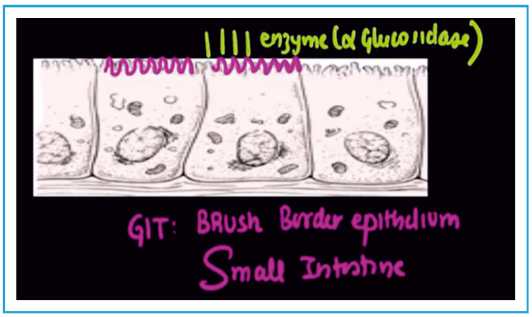
Contraindications
- Metformin is contraindicated in renal disease
  - High dose: Lactic acidosis
- GFR: <30 ml/min
- Serum creatinine>1.5 mg/ml

Important Information
- Drugs in DM which are safe or don't require dose reduction in renal disease
  - **Mnemonic:** Let's Try ATP
    - → Linagliptin
    - → Teneligliptin
    - → Albiglutide
    - → Dulaglutide
    - → Pioglitazone/Rosiglitazone

02. α Glucosidase inhibitors

01:03:46

- It includes
  - Acarbose
  - Voglibose
  - Miglitol



α Glucosidase enzyme is located on the brush border epithelium of small intestine

↓

Complex food molecules are broken down into simple molecules

↓

Crosses intestinal cells

↓

Absorbed into the blood

- After meal: Glucose absorption is reduced with these drugs
- Taken before meals: Reduce the risk of Postprandial hyperglycemia
- Route: Oral
- Weight: Neutral
- Hypoglycemia: No risk

Acarbose

- Uses of Acarbose: Approved for type 1 and type 2 DM
- Side effects:
  - Flatulence
  - Malabsorption/GIT upset
- C/I: GIT infections
  - Inflammatory bowel disease (Ulcerative colitis/Crohn's disease)
- Patient of hypoglycemia on acarbose like drug

Insulin or Sulfonylureas

↓

Hypoglycemia

↓

Sucrose is consumed while taking acarbose

↓

Sucrose will not be effective in correcting hypoglycemia

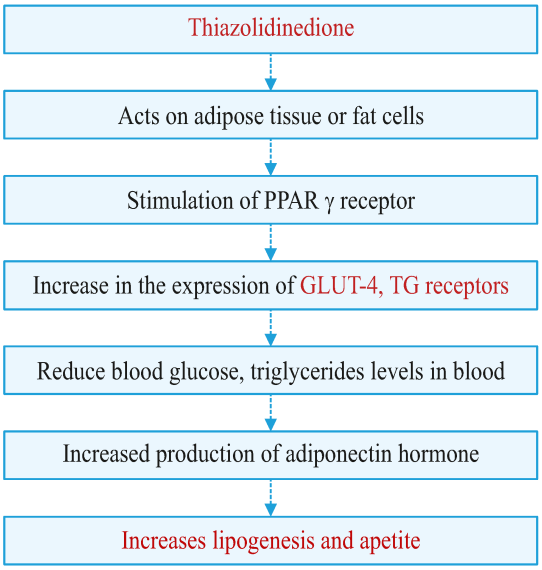
  - Acarbose inhibits the degradation of sucrose into monosaccharide
  - Precaution: Pure glucose or pure fructose (honey, fruit juices) are recommended

03. Thiazolidinedione

01:12:36

- Ends with the word glitazone

MOA

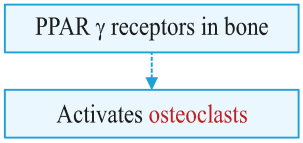


- PPAR: Peroxisomal proliferator activating receptor
- These drugs reduce the resistance of insulin on adipose tissue
- Only act in the presence of insulin
- Only approved in type 2 DM
- Drugs include
  - Troglitazone
  - Pioglitazone
  - Rosiglitazone
- ROA: Oral
- Weight: Gain
- Hypoglycemia: No response

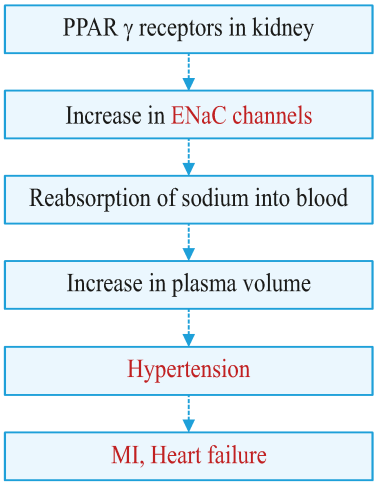
Troglitazone	• Banned: Hepatotoxic
Rosiglitazone	• Banned: Increased risk of MI/Heart failure
Pioglitazone	• Available in India • Warning: Increases the risk for urinary bladder cancer • Hepatotoxic drug and increases the risk of MI and heart failure • Safest drug in renal failure • Pharmacokinetics ○ Metabolism: CYP3A4 enzyme

Side effects-All Glitazones

1. Increased risk of osteoporosis, Increased risk of fractures



2. Has antidiuretic effect



- Contraindication: Heart failure

Important Information

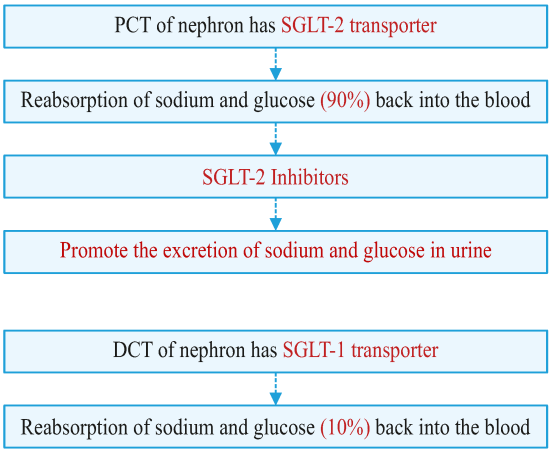
SGLT 2 inhibitors and pioglitazone increases the risk of fractures

- SGLT-2 Inhibitors: Has diuretic effect
  - Treat heart failure
- PPAR γ agonists: Pioglitazone
  - Used in type 2 DM
- Telmisartan has PPAR γ agonist property
  - Angiotensin receptor blocker
- PPAR α agonists: Fibrates
  - Treat dyslipidemia
- Dual PPAR α and γ agonists: Saroglitazar
  - Treat diabetic dyslipidemia

04. SGLT-2 Inhibitors

01:25:44

- Sodium glucose transporter: SGLT
  - Location: Nephrons
- Has diuretic effect
- Produce glycosuria



- **Drugs** (-gliflozin)
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Remogliflozin
  - Ertugliflozin

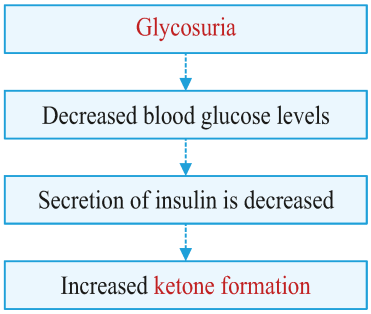
  } SGLT-2 inhibitors
  - Sotagliflozin: Both SGLT-1 and SGLT-2 inhibitor
- ROA: Oral
- Weight: Loss

Beneficial effects

- Promote glucose excretion → Decrease in blood glucose → Treat type 2 DM
- Produce Na^+ excretion → Reduce plasma volume (diuretic action)
- Antihypertensive effect
- Cardioprotective effect - approved for chronic heart failure

Side effects

- Urinary tract infections
  - Other Name: Urogenital infection
  - Increased risk for bacterial or mycotic infection
  - Increased risk of fournier's gangrene
- Increased risk of osteoporosis
  - Ca^{2+} excretion (decreased bone density)
- Increased risk of diabetic ketoacidosis



Comparision

PYQ: INICET 2023

Pioglitazone, Rosiglitazone	Canagliflozin, Dapagliflozin, Empagliflozin, Sotagliflozin
Increased risk of osteoporosis (Fractures)	Increased risk of osteoporosis (Fractures)
Antidiuretic effect	Diuretic effect
Contraindication: Chronic heart failure	Treat chronic heart failure

Additional Drugs For Type 2 DM 01:37:03

Colesevelam	• Bile acid sequestrant ○ Decrease in blood glucose levels (Decreases HbA1c) • Use: Type 2 DM

Bromocriptine	• Stimulation of dopamine D2 receptor in hypothalamic-pituitary axis
	  ○ Reduction in the secretion of pituitary hormones (Counter regulatory to insulin)
	  → Produce hypoglycemia
	• Approved for type 2 DM
	• Taken early morning

Complications of DM

01:40:28

Diabetic gastroparesis

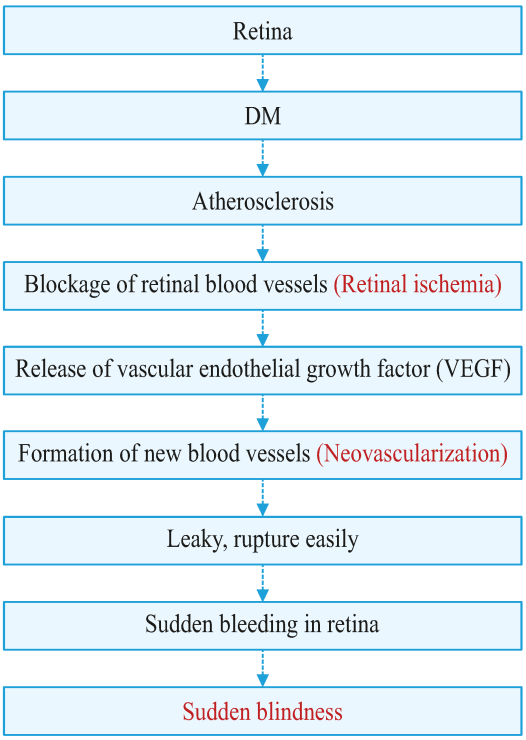
- Due to drugs and nephropathy
  - Pramlintide
  - GLP-1 analogue
- Treatment: Erythromycin
  - Increase motilin receptors on stomach (Increase gastric motility)

Diabetic diarrhea

- Reduced fluid and electrolyte absorption from large intestine
- **Drug:** Clonidine

Clonidine
↓
Stimulates α 2 receptors in the intestine
↓
Reduce excretion of Na/Cl- in feces
↓
Reduce the risk of diarrhea

Diabetic Retinopathy



- Treatment: Anti VEGF
  - **Mnemonic:** BRAP
    - → Bevacizumab
    - → Ranibizumab
    } Monoclonal antibodies against VEGF
    - → Aflibercept: Decoy receptor of VEGF
    - → Pegaptanib: Aptamer
  - ROA: Intravitreal injection

Diabetic Neuropathy

- Treatment: Three classes of drugs
  - Antiepileptic drugs
    - → Pregabalin: DOC for diabetic neuropathy
    - → Gabapentin
    - → Carbamazepine
    - → Topiramate
  - Antidepressants
    - → Duloxetine
    - → Amitriptyline
    - → Nortriptyline
  - Miscellaneous drugs
    - → Mexiletine (Anti arrhythmic drug)
- New drug: Epalrestat
  - Aldose reductase inhibitor
  - Inhibits the conversion of glucose to sorbitol

3 THYROID AND ANTI-THYROID DRUGS

Thyroid Hormones

00:00:12

PYQ: FMGE 2021

- T_4: Levothyroxine
- T_3: Liothyronine

T_4	T_3
Has 4 iodine molecules	Has 3 iodine molecules
Major form/ more in blood	Less in blood
Prohormone	Active form
Longer duration of action	Fast onset of action
• Given orally ○ Taken empty stomach → Increases absorption • DOC:chronic hypothyroidism-Oral ○ Myxedema coma-I/V	• IV (faster) ○ DOC for myxedema coma

- Peripheral conversion of T_4 to T_3
  - 5' Deiodinase

Thyroid Physiology

Physiology

00:05:08

In Thyroid follicle

↓

Colloid has blood vessels

↓

Iodine enters thyroid follicle

↓

Transporter: Sodium Iodide symporter

↓

Gets converted into T_3 & T_4 by TPO enzyme(thyroid peroxidase)

↓

Converts iodide into iodine molecule (oxidation)

↓

Iodine attaches on tyrosine and forms MIT, DIT (organification)

↓

MIT + DIT = T_3

and

DIT + DIT = T_4

Known as coupling

↓

Gets released into blood (rate limiting step)

↓

T_3: active form

and

At the level of cells, T_4 gets converted to T_3 (Peripheral conversion)

Antithyroid Drugs

00:09:54

1. Sodium Iodide symporter ($Na^+ I^-$) inhibitor

- Inhibits iodine entry into thyroid
  - Thiocyanate,
  - Perchlorate,
  - Nitrates
  - Pertechnate,
  - Floroborates
    - → These drugs are not used

Important Information

- Nitrate, nitroprusside:
  - Used in hypertension
  - Side effect - Hypothyroidism
    - → Inhibit the entry of iodine

2. Thyroid Peroxidase Inhibitors

00:10:52

- Known as: Thionamides
- Inhibits synthesis of T_3 & T_4
- They inhibit thyroid peroxidase enzyme, which in turn inhibits the 3 steps
  - Oxidation
  - Organification
  - Coupling
- 2 types of thionamides:

1. Propylthiouracil (PTU)
2. Carbimazole (Prodrug)

- Methimazole (Active form)

PYQ: FMGE 2021

Propylthiouracil (PTU)	Carbimazole/ Methimazole
Inhibits peripheral T_4 to T_3 conversion	No such side effect
High plasma protein binding	Less plasma protein binding
High placental crossing	Least placental crossing
Side effect:Highly hepatotoxic	Side effect: Less hepatotoxic

Important Information

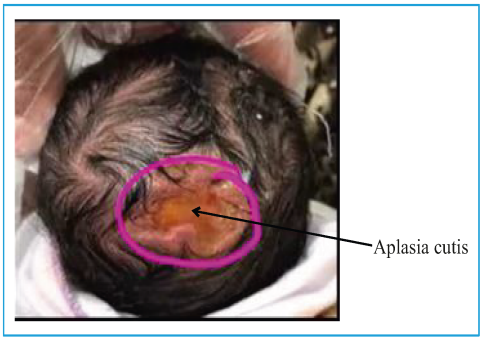
- Ethionamide
  - Used for treatment of TB
  - Side effect: Hypothyroidism

Uses of Thionamides

00:15:23

- Thyroid storm: DOC - PTU
- Hyperthyroidism in pregnancy
  - 1st Trimester: PTU
    - → Contraindicated in 2nd & 3rd trimester
    - → Highly hepatotoxic
  - 2nd & 3rd trimester: Carbimazole or Methimazole

→ Contraindicated in 1st trimester
→ Highly teratogenic
→ Teratogenic malformation: inhibits skin formation - Aplasia cutis



- Chronic hyperthyroidism: Graves, toxic goitre
  - Carbimazole or Methimazole

Side effects

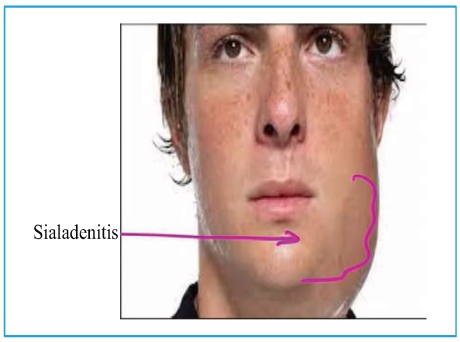
- Sulfa allergy
  - Rashes: Maculopapular rash
  - Bone marrow suppression: Agranulocytosis

3. Oral Iodides

00:18:00

PYQ: FMGE 2022

- Inhibit release of T_3 & T_4 (rate-limiting step)
  - Fastest antithyroid drugs
- Causes vasoconstriction in blood vessels: Thyroid constipation
- Oral iodides are:
  - Na-iodide,
  - Saturated solution of KI (SSKI)
  - Lugol's iodine
    → 5% I_2 + 10% KI solution
- Used in
  - Thyroid storm
  - Reduce the size of thyroid
    → Before surgery
    → Decreased risk of bleeding and laryngeal nerve damage
- Side effects of iodides
  - Sialorrhea: excessive salivation
  - Sialadenitis: Inflammation of salivary glands
    → Mimics Mumps



Radioactive Iodine

00:21:22

- I^{123}
- I^{125}

} Only emit α rays → Used for thyroid scan

PYQ: FMGE 2021

- I^{131}
  - Also emits β rays
  - Destroy thyroid glands
  - Given to treat hyperthyroidism
    → Not fit for surgery: Old aged, heart diseases
- $T_{1/2}$: 8 days
- Contraindicated in <35 years, pregnancy
- S/E: Permanent hypothyroidism
  - Life long T_4 replacement

Drugs Inhibiting Peripheral T_4 to T_3 Conversion

00:23:55

- Inhibits 5' Deiodinase
- **Mnemonic: PPIDA**
  - Propranolol : First drug
  - PTU
  - Iodides
  - Dexamethasone Last drug
  - Amiodarone

  T/t : Thyroid storm (Thyrotoxicosis)

  → 37% iodine
  → S/E: Hypothyroidism

New Drugs

00:25:30

Teprotumumab

PYQ: NEET PG 2022

- Monoclonal antibody
- Blocks IGF-1
- Given in thyroid eye diseases
  - Treatment of proptosis

Thyroid eye disease

Vandetanib, Cabozanitinib

- Tyrosine kinase inhibitor
- Anticancer drugs given in medullary carcinoma of thyroid

4 DRUGS ACTING ON BONE AND OSTEOPOROSIS

- Calcium and phosphates are responsible for bone formation and bone destruction 00:00:36

	Vitamin D3	Parathyroid Hormone	FGF-23
GIT	Increases the absorption of calcium and phosphates	Increases absorption of calcium and phosphates	-
Kidney	Decreases excretion of calcium and phosphates	Increases absorption of calcium and excretion of phosphates	Increases excretion of phosphates
Bone	Mineralisation	Demineralisation	Demineralisation
Serum Ca/PO4	Increases calcium and phosphates in blood	Increases calcium and decreases phosphates	Decreases phosphate levels

- Good Hormone: Vit D3
- Bad Hormones: Parathyroid and FGF-23

Burosumab 00:03:56

- Given in osteoporosis
- Monoclonal antibody
  - Blocks FGF-23
- Given in X linked hypophosphatemic Osteoporosis

Vitamin D3 00:05:12

- Hormone: has receptors
  - Cytoplasmic receptors
- Natural form: Present in plants
  - Vit D2: Ergocalciferol

Enters the liver
↓
25 alpha hydroxylase gets converted into 25 hydroxy D2 (calcidiol), D3 (calcifediol)
↓
Enters the kidney
↓
Adds with 1 alpha hydroxylase and becomes 3-OH (triol)
↓
1,25 (OH2) D2/ D3: Active form
↓
Known as Calcitriol
↓
DOC in renal disease patients

- In animals, D3: Cholecalciferol
  - Pro hormone

- Alfa calcidiol, Doxercalcidiol
  - 25 hydroxylase forms

Vitamin D uses

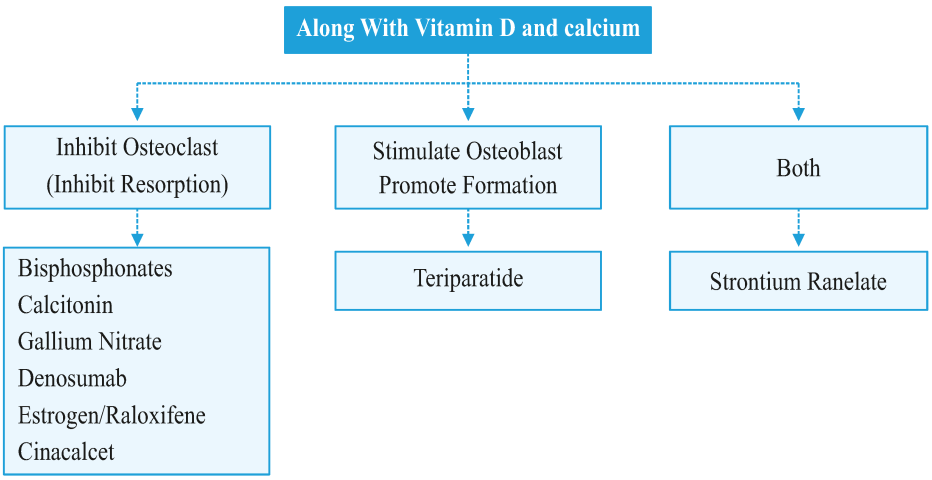
00:10:48

- **Not**: Nutritional rickets
- **Very**: Vitamin D-deficiency rickets
- **Famous**: Familial hypophosphatemia
- **Out**: Osteomalacia/osteoporosis
- **Here**: Hypoparathyroidism
- **Doses**:
  - 0-12 months: 400 IU/ day
  - 1 yr- 70 yr: 600 IU/ day
  - Pregnancy & Lactation: 600 IU/ day
  - >70 yr: 800 IU/ day
- Other synthetic forms of VitD
  - Mnemonic: **DAMP**
    - → Doxercalciferol
    - → Alfacalcidol
    - → Maxacalcitol
    - → Paricalcitol
- Vit D decreases the secretion of Parathyroid
  - Used in hyperparathyroidism
- Calcipotriol (topical): Anti inflammatory
  - Used in Psoriasis, Alopecia areata

Drugs for Osteoporosis

00:14:16

- Reduced bone mineral density
  - Pathological fractures
- These drugs increase bone mineral density



- Osteoclasts: destroy bone
  - Resorption
- Osteoblasts: Forms(anabolic)

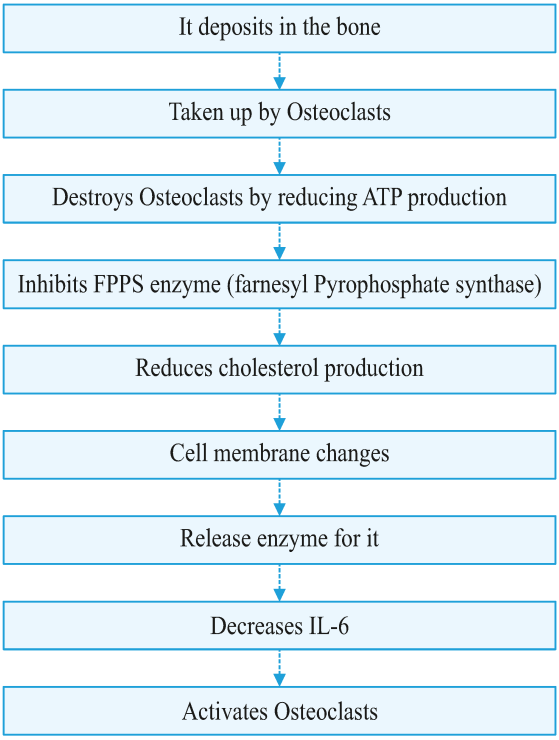
Drugs inhibiting Osteoclasts/Resorption	Drugs stimulating Osteoblast/ Promote formation
• Bisphosphonates • Calcitonin • Gallium Nitrate: not used • Denosumab • Oestrogen/Raloxifene • Cinacalcet	• Teriparatide • Shows anabolic effect • Recombinant form of PTH • New drug: Romosozumab

- Strontium Ranelate-Both Stimulate and inhibits osteocLAST
  - Not available
- DOC: Bisphosphonates
- Teriparatide given in resistant cases

Bisphosphonates

00:20:20

- Ends with Dronate/ Dronic acid
- Structure: PO_4–Ca^{2+}-PO_4
  - Pyro-phosphonate



1st Generation	• Etidronate
	  ○ Not used
	  ○ Increase in risk of osteomalacia
	  ○ Least potent
	  ○ Given OD
	• Tiludronate
	  ○ 10 times more potent

2nd Generation	• Pamidronate
	• Alendronate
	  ○ 100 times more potent
	  ○ Given once weekly
	• Ibandronate
	  ○ 500 times more potent
	  ○ Given once a month

3rd Generation	• Risedronate
	• Zoledronate
	  ○ 1000 times more potent
	  ○ Given once in an year
	  ○ Longest acting

Uses of Bisphosphonates 00:27:40

- DOC in HOP(Mnemonic)
  - Hypercalcemia
    → Malignancy
  - Osteoporosis
    → Postmenopausal osteoporosis
    → Corticosteroids (Cushing's syndrome)
  - Paget's disease of bone
- Decrease the risk of hip, femur and vertebral fractures
- ROA: Given orally
  - Except Pamidronate, Zoledronate-IV/IM
    → Preferred in Hypercalcemia
- Oral Bisphosphonates, causes esophagitis
  - Should give capsules of BPs
  - Should be administered on an empty stomach
    → With plenty of distilled water
    → Don't eat anything
    → Don't lie down for 30 minutes
      – To avoid reflux esophagitis

Adverse effects of bisphosphonates 00:34:25

- Mnemonic: ROSE
- Renal damage
  - C/I in renal failure
  - Denosumab can be Given
- Osteonecrosis of mandible
  - Increase in MMP enzyme
- Increased risk of Subtrochanteric femur fractures
- Esophagitis

	Given Max Up to	Beyond that
Bisphosphonates	10 yrs	Increase the risk of femur fracture
Teriparatide	2 yrs	Increases the risk of Osteosarcoma

Calcitonin

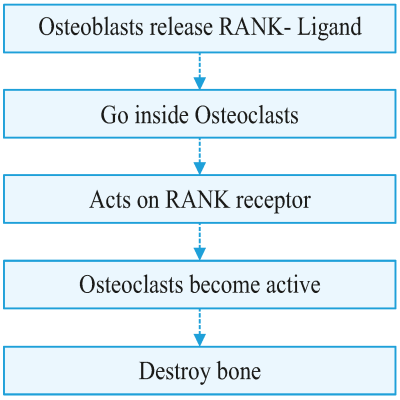
00:37:33

- Hormone synthesised from para follicular C cells of the thyroid
  - Medullary carcinoma of thyroid- calcitonin levels increased drastically
- Marker of Medullary carcinoma of the thyroid
- Inhibits Osteoblasts
- Obtained from salmon fish
  - Known as Salcatonin
- Used in
  - Hypercalcemia (IV)
    - → Calcitonin: Fastest calcium lowering drug
  - Osteoporosis
  - Paget's disease
    - → Intranasal spray
- ROA: IV/ Intranasal spray
- S/E: Allergic reactions, Flu like Syndromes

Denosumab

00:40:56

- Given in Osteoporosis
- Blocks RANK receptor on Osteoclast



- Uses: Mnemonic (HOG)
  - **H**ypercalcemia
  - **O**steoporosis
  - **G**CT Bone/ Osteoclast tumour
- A Renal safe drug
- C/I: Hypocalcemia

Oestrogen, SERM

00:44:03

- Selective oestrogen receptor modulator
  - Raloxifene
  - Bazedoxifene
  - Lasofoxifene
- Oestrogen inhibits RANK receptors
  - By producing Osteoprotegerin
  - And inhibits Osteoclasts
- Used in Postmenopausal osteoporosis

- Due to oestrogen deficiency
- DOC: Bisphosphonates

Cinacalcet

00:46:57

- New drugs
  - Etelcalcetide
  - Evocalcet
- Calcimimetic drugs: mimic calcium

MOA

Calcium acts on Parathyroid glands
↓
Acts on Calcium Sensing receptor
↓
Reduce the production of PTH

- Used in Hyperparathyroidism
  - Inoperable cases only

Teriparatide

00:49:25

- New drug: Abaloparatide
- Recombinant form of PTH

1-34 amino acids of PTH: main active part
↓
Recombinant PTH 1-34
↓
Teriparatide

PTH in low dose and intermittent	High dose: Hyperparathyroidism
↓	↓
Stimulates osteoblasts	Stimulates Osteoclasts
↓	↓
Anabolic form	Destroy bone
↓	
Increases bone formation	

- Given S/C intermittent or weekly injections
- Given in bisphosphonate resistant osteoporosis
- All "TIDE" drugs are peptides
  - Can't be given orally
- S/E: Mnemonic (ROAD)
  - Renal stones
  - Osteosarcoma
    → C/I in Paget's disease and beyond 2 years
  - Increases ALP levels
  - Distal radial fractures

Romosozumab

- New drug for Osteoporosis
- Monoclonal antibody that blocks sclerosing receptor
  - Increases activity of Osteoblast
  - Increases bone formation
    → Anabolic effect

Drugs for Hypercalcemia 00:56:45

- Plenty of saline(6-8L/day) + loop diuretics
  - Increases calcium excretion
    → Acute phase
- Thiazides diuretic is contraindicated
  - S/E: Hypercalcemia
- Maintenance phase:
  - Bisphosphonates
  - Calcitonin
    → Fastest calcium lowering drug
  - Denosumab
    → Most preferred
- C/I: Teriparatide
- Hypervitaminosis D in
  - Cancer
  - Granulomatous disease
    → DOC: Corticosteroids
- Hyperparathyroidism
  - Cinacalcet

Drugs for Hyperphosphatemia 01:00:50

- DOC: Sevelamer
  - Phosphate binding resin
- Lanthanum carbonate
- Calcium carbonate /Calcium acetate
- Aluminium hydroxide 10
- Iron: Ferric citrate, Sucroferric oxyhydroxide
- Niacin (nicotinic acid): Reduces free phosphate levels (Vit B3)
  - Metal salts
  - Chelates phosphate
  - Mnemonic: LACI

5 GONADAL HORMONES

- Other Name: Sex steroids 00:00:08
- Males: Testosterone
  - Other Name: Androgens
  - Intra cytoplasmic receptor
    → Acts on DNA.
- Female: Estrogen
  - Intra nuclear receptors

Sex hormones
↓
Inside the blood
↓
Attaches to a protein
↓
Transported by sex hormone binding globulin

Estrogen 00:01:42

- In female, it is of three types
  - E1: Estrone
  - E2: Estradiol
  - E3: Estriol
- Natural estrogens: Cannot be given orally
  - Has high first pass metabolism in liver
- ROA: Transdermal patches
- Used in hormone replacement therapy

Synthetic estrogens

- ROA: Oral

Steroidal	• It include ○ Ethinyl-Estradiol ○ Mestranol ○ Tibolone: New specific drug
Non-steroidal	• It includes ○ Diethylstilbestrol ○ Hexestrol ○ Dienestrol

- Contraindication: Pregnancy
  - Category X drug
  - Increased risk of vaginal carcinoma
- Male: Increased hypospadias

1. Ethinyl estradiol

- Most commonly used preparation
- Before menopause: Oral contraceptive pill
- After menopause: Hormone replacement therapy

2. **Mestranol**
   - Used as Oral contraceptive pill
     - And in hormone replacement therapy
   - Less commonly used

3. **Tibolone**
   - Not used as oral contraceptive pill
   - Used in hormone replacement therapy
   - Additionally, stimulate the progesterone, testosterone receptor
     - Progesterone: Shedding of endometrium
       → Use: Endometriosis
     - Testosterone:
       → Causes acne, hirsutism in females

4. **Diethylstilbestrol**
   - Treat advance stages of prostate cancer

Estrogen in males
↓
Decreased FSH/LH
↓
Decreased testosterone production

5. **Dienestrol**
   - Available as topical vaginal creams
   - Treat senile (atrophic vaginitis):
     - Occurs in postmenopausal females
     - Deficiency of estrogen

Selective estrogen receptor modulators

00:09:45

- Has both agonist and antagonist actions depending on the organ
- Ends with the word Phen or Fen
- It includes
  - Tamoxifen: Prevent breast cancer
  - Raloxifene: Only prevent breast cancer
  - Toremifene: Treat breast cancer
- Block estrogen receptor in breast tissue
- Treat estrogen positive breast cancer
- DOC: Tamoxifen

Effects the estrogen in other organs

00:11:20

- Breast → Growth of breast cells → Cancer
- Endometrium Growth → Cancer
- Bone → Inhibition of osteoclasts → Increase in bone density → Protect osteoporosis
- Liver → Increase in clotting factor synthesis (2,7,9,10) → Deposition in veins → Deep venous thrombosis/Pulmonary embolism
  - Other Name: Thromboembolism

SERM for Breast Cancer : Tamoxifen, Raloxifen, Toremifene 00:14:06

1. Tamoxifen

PYQ: FMGE 2021

- It is a estrogen receptor antagonist
  - Breast
  - Brain
- Stimulate estrogen receptors in three organs
  - Bone: Reduce the risk of osteoporosis
  - Endometrium
  - Liver
- DOC: ER positive breast cancer
  - Treat and prevent breast cancer
    → Decrease the risk of contralateral breast cancer
- **Side effects:**
  - Increased risk of endometrial cancer
    → Not by raloxifene
  - Liver: Thromboembolism
    → DVT, PE
  - Hot flushes
  - Depression
  - Hepatotoxic drug
  - Cataract (block Cl-channel of lens)
- **Properties/Pharmacokinetics**
  - Active drug : Endoxifen
    → In liver with CYP2D6 enzyme
- Fluoxetine: Antidepressant
  - Class: SSRI
  - Inhibits CYP2D6 enzyme
  - Do not combined with tamoxifen

SERMS for post menopausal osteopetrosis 00:22:16

- Estrogen agonists at bone
- It includes
  - Raloxifene
  - Bazedoxifene: Treat post menopausal hot flushes
  - Lasofoxifene: Treat senile vaginitis
- Post menopausal osteopetrosis

PYQ: FMGE 2021

  - DOC: Bisphosphonates
    → Alendronate
    → Ibandronate
    → Zoledronate

2. Raloxifene

PYQ: NEET PG 2022

- It is a estrogen receptor antagonist
  - Breast: Prevent breast cancer
  - Brain
  - Endometrium: Doesn't increase the risk of endometrial cancer
- Estrogen receptor agonists
  - Bone: Treat postmenopausal osteoporosis
  - Liver
- Side effects in brain
  - Hot flushes
  - Depression
- In liver: Thromboembolism

Other SERMS

00:26:14

Clomiphene	• Other Name: Anti estrogen
	• Blocks estrogen receptor at all organs
	• Estrogen action in the Brain: Stimulates brain → Negative feedback → Decreased production of FSH/LH→ Inhibits ovulation
	• When the estrogen receptors are blocked in the brain it stimulates increased production of FSH/LH. Thus, inducing ovulation
	• DOC: Ovulation inducing agent PYQ: NEET PG 2021 PYQ: FMGE 2021
	  ○ PCOD
	  ○ In Vitro fertilization
	• Side effects
	  ○ Ovarian hyperstimulation
	  ○ Multiple Ovulation : Twins/ Triplets
	  ○ Bleeding (d/t rupture ovary)
	  ○ Shock
	• Increase the risk of ovarian cancer

Drugs for ovulation induction	• **Mnemonic:** Clomifene Loves Growing follicle
	  ○ Clomiphene (DOC)
	  ○ Letrozole: Aromatase inhibitor
	  → Decrease estrogen → Increase FSH/LH
	  ○ Gonadotropin releasing hormone

Ormeloxifene	• Other Name: Centchroman
	• Made in india from CDRI Lucknow
	• Government supply: Saheli, chaya
	• Prevent pregnancy
	• Blocks estrogen receptor at fallopian tube and uterus
	  ○ Decreased motility
	  ○ Inhibit the implantation of embryo
	• Advantages
	  ○ Weekly dose
	  ○ Non steroidal contraceptive drug
	  ○ Inhibits the growth of endometrium
	  → Reduce the risk of menorrhagia
	  ○ Decrease the risk of breast cancer
	• Disadvantage
	  ○ Weak
	  ○ High failure rate
	• Side effect: Hypomenorrhea

Ospemifene	• Approved for the treatment of senile vaginitis
	  ○ Drugs include: HOLD
	  → Hormone replacement therapy
	  → Ospemifene
	  → Lasofoxifene
	  → Dienestrol

Fulvestrant	• Estrogen receptor antagonist
	• Other Name: Selective estrogen receptor down regulator(SERD)
	• Approval of new drug: Elacestrant
	• Use: Tamoxifen resistant ER+ breast cancer
	• Side effects:
	  ○ Hot flushes
	  ○ Osteoporosis
	  ○ Depression

Aromatase Inhibitors

00:40:08

Pre menopausal women

↓

Ovary produce sufficient estrogen

Post menopausal female

↓

Testosterone is converted to estrogen by aromatase enzyme

- DOC: ER+ breast cancer in postmenopausal women

00:42:30

- Aminoglutethimide: Not used -1st Gen-Nonsteriodal + Irreversible
- Formestane -2nd Gen-Steriodal + Reversible
- 3rd Gen -2 types-Steriodal & Non steriodal
- Exemestane-steroidal type 1
- Non Steriodal (type 2)-Letrozole, Vorozole, Anastrozole (Potent)
- Letrozole: Drug for postmenopausal breast cancer
  - T1/2: 40hrs
  - Ovulation inducing agent in PCOD

Adverse effects

- Worsen post menopausal symptoms
  - Hot flushes
  - Osteoporosis
  - Depression
- Tamoxifen: Decreased the risk of osteoporosis

Progestins

00:45:40

- Endogenous natural molecule: Progesterone
- It can be natural or synthetic
  - Natural: Not used
    → Not absorbed orally
- Use: Synthetic progestins
  - Four types

	Estrogenic action	Androgenic action	Drugs
Pregnanes: Pure progestins	No	No	• Medroxyprogesterone acetate (IM Depot) • Injectable contraceptive • Once/3 months
Estranes	Yes	Yes (Acne,hirsutism)	• Norethindrone, Norethindral
Gonanes	Yes	No	• Levonorgestrel • Desogestrel • Norgestimate • Gestodene
Nor-progestins	Block (to treat Endometriosis)	Block (to treat Acne, Hirsutism)	• Cyproterone • Drospirenone • Diuretic: Spironolactone

Drugs blocking the progesterone receptor

00:52:17

PYQ: INICET 2022

Mifepristone

- Other Name: RU 486
- Blocks progesterone and glucocorticoid receptors
- Uses
  - Medical abortion
    → Along with misoprostol
  - Emergency contraceptive (Off label use)
    → Once a month contraceptive
  - Treat fibroids and Cushing disease

Selective Progesterone receptor modulator

Ulipristal

- Emergency contraceptive pill
  - Other Name: Post coital pills
- Dose: 30 mg once within 5 days of unprotected sex

Androgens

00:57:04

- Major form in male: Testosterone
  - Responsible for spermatogenesis
    → Other Name: Primary sexual development
  - Dihydrotestosterone
    → More potent
    → Increase prostate growth
    → Causes alopecia
    → Secondary sexual characters development
- 5 alpha reductase enzyme converts testosterone to dihydrotestosterone

Synthetic Androgens

17 alkyl substituted testosterone	• Methyltestosterone
	  ○ ROA: Oral
	  ○ Side effects: Cholestatic jaundice

Testosterone undecanoate	• IM depot injection
	• Absorbed from the lymphatics and reaches the blood
	• Uses:
	  ○ Cachexia
	  → HIV positive
	  → Cancer

Anabolic steroids	• Anabolic to endocrine effect
	• **Mnemonic:** NO Stamina
	  ○ Nandrolone
	  ○ Oxymetholone
	  ○ Stanozolol

- C/I: Sports (dope drugs)

Adverse effects 01:02:36

- **Mnemonic:** SATHIA
  - **S**tunting: Premature epiphyseal closure
  - **A**cne
  - **T**esticular atrophy
    → Reduced spermatogenesis
    → Suffers from azoospermia
  - **H**irsutism
  - **I**ncreased hepatic cancer
  - **A**lopecia in males

Danazol

- Stimulate testosterone receptor
- Blocks estrogen receptor
  - Treat endometriosis
  - Fibroids
  - Leiomyoma
- Use: Hereditary angioneurotic edema
- Side effects in males: Azoospermia
- Female: Acne, hirsutism

Hereditary angioneurotic edema 01:07:05

- Genetic deficiency of C1 esterase inhibitor enzyme
  - Over production of bradykinin

High molecular weight kininogen bound with kallikreinin
↓
Production of bradykinin due to the breakage of big molecule
↓
Acts on B2 receptors

- Drugs
  - C1 esterase inhibitor
  - Testosterone
  - Danazol
  - Ecallantia and lanadelumab: Inhibits kallikreinin production
  - Icatibant: Blocks B2 receptor

Anti Androgens

Ketoconazole and Abiraterone	• Antifungal agent • Inhibit the synthesis of testosterone
Finasteride and dutasteride	• Inhibit 5 alpha reductase enzyme PYQ: FMGE 2021

Flutamide	• Androgen receptor blocker
	• Other drugs include
	  ○ Bicalutamide
	  ○ Enzalutamide
	  ○ Nilutamide
	  ○ Spironolactone: Diuretic
	  ○ Cyproterone

Uses

- All drugs treat prostate cancer in males
- Treat hirsutism in females
- Additionally
  - Finasteride, Dutasteride
    → Treat BPH
    → Alopecia in males

Side effects

- Gynecomastia
- Impotence

Drugs for androgenic alopecia

01:17:05

- Male pattern baldness
- Drugs include
  - Minoxidil (Vasodilator)-2-5% topical cream
  - Finasteride/Dutasteride (5 alpha reductase inhibitor)
    →Oral drug

Drugs for Hirsutism

- Facial hair growth
- Three drugs
  - Oral contraceptive pills
  - Antiandrogen drugs: Cyproterone
  - Eflornithine: Topical depilator (Hair remover)
    → MOA: Ornithine decarboxylase inhibitor
    → Use
      - Hirsutism
      - Sleeping sickness

Drugs for post menopausal hot flushes

- Drugs: High Blood Pressure
  - Hormone replacement therapy
  - Bazedoxifene
  - Paroxetine (SSRI)

- Other drugs: Off label use
  - Fluoxetine
  - Citalopram
  - Clonidine
- New drug: Fezolinetant - Blocks neurokinin 3 receptor

Drugs for Erectile dysfunction (Impotence)

01:22:56

- **Mnemonic:** PAPA Y Not Kinky

Phosphodiesterase 5 inhibitors	• It includes
	  ○ Sildenafil
	  ○ Tadalafil
	  ○ Avanafil
	  ○ Vardenafil
	• ROA: Oral
	• Side effects of sildenafil
	  ○ Blue green color blindness
	  ○ Hypotension, Headache

Alprostadil	• Prostaglandin E1 • ROA: Cavernosal injection
Phentolamine/Papaverine	• Vasodilator • ROA: Cavernosal injection
Apomorphine	• ROA: Cavernosal injection

Off label use drugs

- It includes
  - Yohimbine
  - Naltrexone
  - Trazodone (Antidepressants) PYQ: FMGE 2022
    → Causes benign erection
    → Side effect: Excessive/painful pineal erection (Priapism)
  - Ketanserin: Serotonin blockers

6 HPA AXIS HORMONE

- **HPA:** Hypothalamic pituitary axis 00:00:07
- All hormones have GPCR except
  - Growth hormone, Prolactin - JAK STAT receptors
- **Hormones**
  - GH and related hormones
  - Somatostatin
  - Dopamine agonist
  - GnRH, FSH and LSH
  - Oxytocin and related drugs

GH and related hormones 00:01:22

- Hypothalamus releases GnRH
- **Acts on pituitary:** Releases GH
- **GHiH:** Inhibits GH release
  - Somatostatin ,Dopamine.
- **GH**
  - Acts on liver
  - Receptors: JAK STAT receptors
  - Activates liver
  - Releases IGF-1 (somatomedin-C)
    → Promotes growth of muscles and bones by binding to tyrosine kinase receptor

Growth hormone releasing hormone 00:03:42

- **Synthetic forms- S/C Injection**
  - Sermorelin: Used for diagnosis of dwarfism (GH deficiency) PYQ: FMGE 2021
  - Tesamorelin: Treatment of lipodystrophy in HIV positive patients
- These are peptide hormones (can't be given orally)
- Given by Injections (Subcutaneous)

Growth Hormone 00:05:47

- **Synthetic form:** Somatropin
- Given as SC injection
- TOC for dwarfism (should be given before Epiphyseal closure)
- **Other uses:** Mnemonic- AMP
  - **A**IDS related wasting syndrome (cachexia)
  - **M**alabsorption in short bowel syndrome
  - **P**remature infants

- **Side effects:** Mnemonic- **CHILS**
  - **Carpal tunnel syndrome**
    → Due to excessive growth of tissues
    → Median nerve entrapment occurs
  - **Hyperglycemia**
    → Hormones of the hypothalamus and pituitary produce opposite action of insulin
  - **I**ncreased Intracranial pressure (contraindicated in head injury)

- **L**ymphoma (contraindicated in malignancy)
- **S**lipped capital femoral epiphysis

IGF-1

00:09:37

- Insulin like growth factor
- **Synthetic form:** Mecasermin
- Combined with rinfabate (IGF binding protein)
- Given as SC injection
- DOC for dwarfism in growth hormone resistant cases -Mecasermin
- **Side effect:** Hypoglycemia

Inhibitors Hormones

00:11:20

- Somatostatin
- Dopamine

Somatostatin	Dopamine
Hypothalamus releases somatostatin ↓ Inhibits hormone releases from the pituitary ↓ Reduces release of all hormones (GH, TSH, ACTH) >>> prolactin	Hypothalamus releases Dopamine ↓ Mainly inhibit Prolactin >>>all hormones

- **In acromegaly:** Somatostatin
- **In prolactinemia:** Dopamine like drugs
- Somatostatin Acts on SST receptors:
- Dopamine Acts on D2 receptor:

} Gi type of GPCR

Pituitary Tumors

00:13:31

GH excess (Acromegaly)

- **1st treatment:** Surgery (transsphenoidal pituitary removal)
- **2nd treatment:** Somatostatin (DOC)
  - Octreotide
  - Lanreotide
- If resistant to somatostatin use- pegvisomant (Blocks GH receptors) PYQ: NEET PG 2021

Prolactinomas

- 1st treatment: Dopamine agonist
  - Cabergoline (DOC)
  - In pregnancy: Bromocriptine is used
  - Still resistant: Surgery should be done

Pegvisomant

00:16:32

- GH receptor antagonist
- Used in acromegaly resistant to octreotide
- Given by SC injection
- Contains PEG (polyethylene glycol) - Makes the drug longer acting
- Side effect: Visual disturbance

Somatostatins: Inhibitory hormones 00:18:18

- Produced by
  - Delta cells: Present in HPA
  - GIT: Decreases GI hormone production

- **Drugs** (end with - reotide)
  - **Octreotide**
    → Contains 8 amino acids
    → SC injection
    → t1/2: 90 mins
  - **Lanreotide**
    → Intramuscular depot injection
    → Longest acting
  - **Vapreotide**
  - **Pasireotide:** Reduces ACTH (specific)
  - Specifically approved for Cushing's disease

Uses of Octreotide 00:21:24

- Mnemonic: **IDEAS**
- **I**nsulinoma (DOC), glucagonoma and gastrinoma: PNET (Pancreatic Neuro Endocrine Tumors)
- **Diarrhea:** Carcinoid, ViPoma, HIV and cancer induced (secretory diarrheas)
- **E**sophageal varices bleeding
  - For acute variceal bleeding: DOC is Terlipressin > Octreotide
- **A**cromegaly
- **S**hort Bowel syndrome (To prevent secretory diarrhea)

Side effects of Octreotide

- Gallstones (due to less motility of gall bladder by reducing CCK hormone production)
- Hypothyroidism

New drugs

- Radio isotope is attached with Octreotide
- **Drugs**
  - Yttrium 90 with Octreotide
    → Emulsions radioactive waves
    → Used for PET scan for PNET Tumors diagnosis
  - Lutetium containing octreotide (treatment of PNET tumor) - Lu-DOTATE

Dopamine (D2) Agonist 00:26:40

- Can be given orally and also IV
- **Drugs**
  - Bromocriptine (safe in pregnancy) PYQ: FMGE 2021
  - **Cabergoline**
    → Most potent
    → Most effective
    → Effective in resistant cases of bromocriptine
  - **Pergolide**
    → Ergot
    → Got banned as it was causing cardiac valve fibrosis
  - Quinagolide (non ergot)

- **Uses of bromocriptine and cabergoline**
  - DOC for prolactinomas
    - → Features
      - – Galactorrhea
      - – Amenorrhea
      - – Visual abnormalities (d/t compression of optic nerve)
    - → Overall DOC: Cabergoline
    - → DOC in pregnancy: Bromocriptine
  - Parkinson's disease
  - Suppress lactation

- **Adverse effects**
  - Mnemonic: **PPPEI**
  - **P**UKE: Nausea and vomiting
  - **P**ostural hypotension
  - **P**sychosis
  - **E**rgotism: Fingers rot
  - **I**nflammation leading to fibrosis
    - → Cardiac valve fibrosis
    - → Peritoneal and pleural fibrosis

Gonadotropin Releasing Hormones

00:31:51

- Pituitary releases gonadotropins
- 2 types of gonadotropins
  - **FSH**
    - → In males: Spermatogenesis
    - → In females: Growth of Graafian follicle
  - **LH**
    - → In males: Increases testosterone
    - → In females: Promotes ovulation

- **GnRH**
  - Stimulates release of gonadotropins
  - Also Decreases gonadotropins
  - Released in pulsatile manner: Stimulators action
  - Releases in a continuous manner: Inhibitory action
    - → Desensitisation of gonadotropins (> 7 days)

GnRH agonists

00:35:38

- **Human form:** Gonadorelin
  - Shortest acting
  - Rarely used

- **Recombinant GnRH**
  - Also called super agonists
  - 1000 times more potent

- **Drugs**
  - → Goserelin (SC injection and SC implant)
  - → Histrelin (SC injection and SC implant)
  - → Buserelin (SC injection and SC implant)
  - → Triptorelin (IM injection and IM depot)
  - → Leuprolide (given by all routes)
- New drug: Nafarelin (nasal spray)

Uses-GnRH Agonist.

- Intermittent injection: Increase FSH and LH
  - Treatment of azoospermia (male Infertility)
  - Anovulation (female Infertility)
  - DOC in delayed puberty
- Continuous injection: Decrease FSH and LH (after 7 days)
  - DOC for prostate cancer
  - Endometriosis
  - Leiomyoma
  - DOC in precocious puberty

Adverse effects

00:41:08

- **Pulsatile stimulation**
  - Ovarian hyperstimulation
    - → Increased size: Pain in the abdomen
    - → Rupture of the ovary: Bleeding
- **Continuous stimulation**
  - Postmenopausal symptoms
    - → Hot flushes
    - → Osteoporosis
    - → Depression
  - Initial 7 days
    - → High FSH and LH (dangerous in prostate cancer) - Initial flare-up
    - → After 7 days, gonadotropins level falls

Important Information

- Continuous stimulation is never given beyond 6 months due to risk of Osteoporosis

GnRH Antagonists

00:44:57

- Only blocks gonadotropin receptors
- Only decrease FSH and LH
- **Advantage:** No initial flare up reactions
- End with -relix
- **Drugs**
  - Treatment of prostate cancer
    - → Cetorelix
    - → Ganirelix

- In vitro fertilization
  - → Degarelix
  - → Abarelix
- **New drug:** Elagolix
  - → Decrease estrogen production
  - → Treatment of Endometriosis (pain)

Gonadotropins

00:47:27

- 2 types
  - FSH
  - LH
- **Another gonadotropin:** Beta HCG (similar to LH)

Gonadotropin preparations

- Menotropins or HMG (Human menopausal gonadotropins)
  - FSH + LH--- Obtained from the urine of postmenopausal females
- **Urofollitropin:** Pure FSH
- **Recombinant human FSH:** Follitropin Alpha
- **Recombinant human LH:** Lutropin Alpha
- **Recombinant HCG:** Choriogonadotropin Alpha
  - Previously, Beta-HCG was Obtained from urine of pregnant women

Uses

- Treatment of female Infertility and during in vitro fertilization
- Treatment of male Infertility

Oxytocin and Uterine Stimulants

00:51:17

- Stimulate uterus
- Receptor of Oxytocin in the uterus: GPCR
- Contracts myometrium and helps in delivery
- Hence, given for induction of labor
- Also used to stop postpartum hemorrhage
- **Drugs**
  - Oxytocin
    - → IV
    - → DOC in induction and augmentation of labor
    - → DOC to control postpartum hemorrhage
    - → Dose:
      - 6 milli IU IV over 40 mins (max 40 milli IU) for induction of labor
      - 10 milli IU for PPH
  - Carbetocin
    - → Longer acting form of oxytocin
    - → Can be given as IM and IV
  - **Carboprost**
    - → Prostaglandin F2 alpha
    - → Given to control PPH in oxytocin resistant cases (DOC)
    - → Absolutely contraindicated to induce labor (may cause Fetal hypoxia)

- **Ergometrine and Methylergometrine**
  - → Methylergometrine also called methergine
  - → Control PPH in Oxytocin resistant
  - → Can be given IM
  - → Absolutely contraindicated to induce labor

Carboprost

- Contraindicated in asthma
- Dose: 250 mg IV
- Maximum 8 Injections can be given per day
- Max dose per day: 2000 mg IV

Tocolytics and Uterine Relaxants

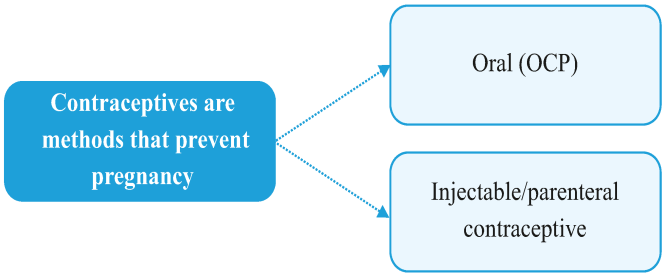
00:58:00

- Given in Premature delivery to delay labor
- **Side effect:** Risk of postpartum hemorrhage
- **Drugs**
  - **Atosiban:** Oxytocin receptor antagonist
  - **Beta 2 agonist**
    - → Ritodrine
    - → Isoxsuprine
    - → Salbutamol
  - **CCB**
    - → Nifedipine
    - → Diltiazem
  - **Halothane**
    - → General anesthetic
    - → Preferred in surgeries where the uterus needs to be relaxed
      - – Caesarean section
      - – Internal version of fetus
  - Mnemonic: **ABC**

Miscellaneous Drugs with tocolytic action

- NSAIDs-Indomethacin
- Magnesium sulfate
- Cardio safe tocolytic: Atosiban

7 CONTRACEPTIVES



Oral contraceptives

00:45:00

	Combined OCP	Progesterone-only pill (POP)	Emergency Contraceptive Pill
A.k.a	-	mini-pill	post-coital pill
Composition	Estrogen + Progesterone	Progesterone	Many options
MOA	All actions • Inhibits ovulation (main) • Inhibits fertilization • Inhibits implantation of embryo • Produces cervical mucous thickening	Cervical mucous thickening	Inhibits embryo implantation
Efficacy in pregnancy prevention	98 -99.9 %	96 -98%	<95%
Failure rate	1%	2-4%	5%
FSH	Suppressed	-	-
LH	Decreased	Decreased	Decreased
Cervical mucous	Thick	Thick	-
Endometrium	Hypertrophy	Secretory ⇓ Shedding (breakthrough bleeding)	-

Important Information

- Overall the most effective contraceptive is implanon (injectable) > COCP
- Parental contraceptives produce atrophy of the endometrium

Combined OCP

00:08:30

Drug of choice

- Newly married couple
- After molar pregnancy

Mechanism of action

- Main action: Inhibits ovulation
- Ovulation resumes after approximately 90 days for 90% of women from the day of stopping COCPs

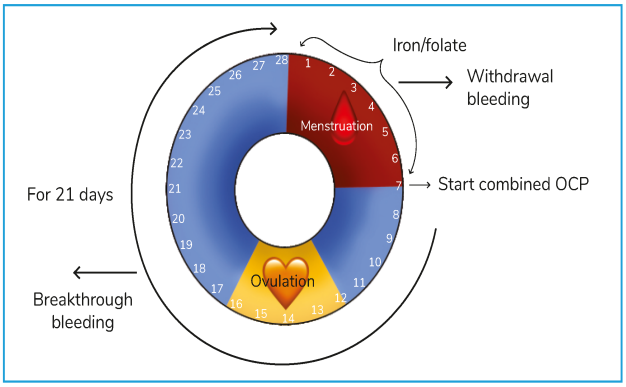
Combined OCP

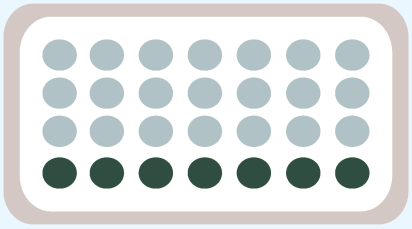
Estrogen	+	Progesterone
Most common form of estrogen used: Ethinyl estradiol > mestranol Dose of ethinyl estradiol 1. 50 µg: Standard dosage - Increases the risk of breast cancer 2. 30 µg: Low dose estrogen 3. <20 µg: Very low dose estrogen		Adding progesterone to estrogen shows synergism Reduce the risk of endometrial cancer Side effect: Breakthrough bleeding

Administration:

00:15:30

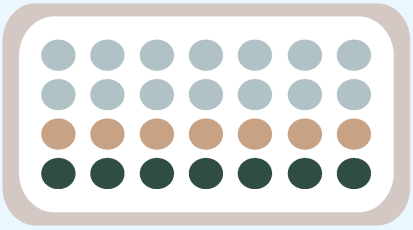
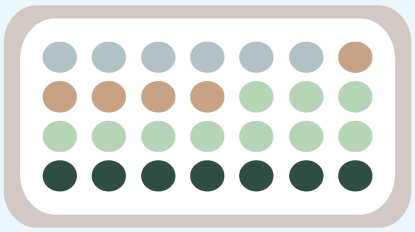
- Single tablet (E+P) given for 21 days
- Remaining 7 days: Iron and folic acid tablets
- The female will suffer withdrawal bleeding in these 7 days
- Side effect: Possible bleeding during first 21 days due to progesterone: Breakthrough bleeding
- Breakthrough bleeding is prevented by giving a lower dose of progesterone: Biphasic and triphasic pills





Monophasic pills (2 colors)

- 1st colour (Light) → E+P: Constant dose 21 days
- 2nd colour (Dark) → Iron and folic acid tablets 7 days

	**Biphasic pills (3 colors)** • 1st colour - E + low dose P for 10 days • 2nd colour - E + normal dose P for 11 days • 3rd colour - Iron and folic acid tablets for 7 days
	**Triphasic pills (4 colors)** • 1st colour - E + very low dose P for 7 days • 2nd colour - E + low P for 7 days • 3rd colour - E + normal dose P for 7 days • 4th colour - Iron and folic acid tablets for 7 days

Other contraceptive pills

- Estrophasic → Gradually increase the dose of estrogen
- Extended cycle pills are given for >21 days.

Precautions following a dose of OCP are missed

- **Missed one dose of OCP** → Take the missed dose as soon as possible or take 2 doses the next day and continue the rest of the schedule
- **Missed 2 consecutive doses** → Stop taking the rest of the pills and use another method of contraception for the rest of the month.

Combined OCP (E+P) pills provided by the Indian government 00:25:25

 Mala-N	**Mala-N** PYQ: INICET 2020 • Contains ○ Ethinyl estradiol (30 µg) ○ Norethisterone (1000 µg) • Available in hospitals and free of cost
 Mala-D	**Mala-D** • Contains ○ Ethinyl estradiol (30 µg) ○ D-Norgesteral (300 µg) • Available in chemist shops and should be purchased

Non-contraceptive benefits of OCP pills 00:28:00

- Reduces risk of the following conditions

B	Benign breast disease (fibrocystic disease)
E	Ectopic pregnancy
N	• Neoplasm • Reduced risk ovarian cancer, uterine cancer and colorectal cancer • Do not increase the risk of breast cancer
E	Endometriosis
F	Fibrosis
I	Iron deficiency anemia/irregular menstruation
T	Tension: Premenstrual tension syndrome
S	Sickle cell crisis (progesterone component)
Of	Osteoporosis
Ocp	Ovarian cyst
Pills	Pelvic inflammatory disease

Adverse effects of OCP 00:32:20

Mild	Moderate	Severe
• Most common - Nausea > vomiting • Oedema • Recurrent headache (migraine) • Mastalgia • Abnormal breakthrough bleeding	• Acne • Weight gain • Melasma (chloasma)	• **Cardiovascular disease risk is increased** ○ Thromboebolism (MI, stroke and PVT/PE) ○ Risk is higher for smokers and women over 35 • **CNS: Depression** • **Cholestatic jaundice** ○ Contraindicated in active liver disease, porphyria and jaundice • **Cancer** ○ Cervical cancer ○ Hepatocellular cancer/ hepatic adenoma ○ Avoid if these symptoms are pre-existing in the patient

- OCPs are stopped if they cause moderate to severe adverse effects

Drug interactions of OCP

00:38:00

Rifampicin

- Rifampicin is CYP enzyme inducer — PYQ: FMGE 2021
- Estrogen is inactivated by CYP3A4
- Combining OCPs with rifampicin leads to contraceptive failure

Antibiotics

- Drugs - Tetracycline, ampicillin, doxycycline and amoxicillin
- Antibiotics kills GIT bacteria - GIT bacteria is necessary GIT absorption or enterohepatic absorption of estrogen
- Combining these antibiotics with OCPs lead to contraceptive failure

Progesterone Only Pills

00:40:48

Advantage of POP over OCP

- Preferred in: PYQ: NEET PG 2021
  - Lactating females
  - Seizure patients
  - Sickle cell disease patients
  - Smokers

Disadvantage of POP

- High failure rate (2-4%)

Emergency contraceptive pills

00:42:50

- Also known as post-coital pills as they are taken after unprotected sexual intercourse
- These should never be taken as regular contraceptives due to the high failure rate (>5%)

Mechanism of action

- Inhibits the implantation of the embryo and also decreases the risk of ectopic pregnancy

How to give ECP?

Combine OCP (E+P)

- Also known as Yuzpe method
- 2 pills of OCP - 2 doses 12 hours apart
- As early as possible after unprotected sexual intercourse
- Most effective upto 72 hours

Levonogesteral (only P) — PYQ: FMGE 2023

- Taken as either a 1.5g one tablet or 0.75 mg 2 tablets 12 hours apart
- Most effective upto 72 hours

Uliprital (blocks P)

- Also known as anti-progestin
- Taken once as a a 30 mg tablet
- Most effective between 72 to 120 hours of sexual intercourse (within 3-5 days)

Injectable (parenteral) contraceptives

00:49:13

- Contains progesterone only and given by injection or implants

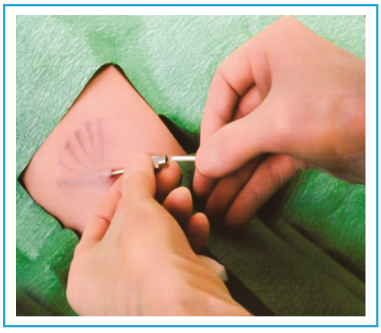
Name	Drugs	Effective duration
DMPA (depot medroxyprogesterone acetate)	IM→ 150 mg	Once in 3 months
NET-EN (norethindrone enanthate)	IM→ 200 mg	Once in 2 months

Implants

Name	Drugs	Effective duration
Norplant • Levonorgestrel • Longest acting	Subcutaneous implant ⇓ Madeup of sialistic rods (non-biodegradable)	5 years
Implanon • Etonogestrel • Lowest failure rate	Subcutaneous implant ⇓ Madeup of sialistic rods (non-biodegradable)	3 years
Uniplant • Nomegestrol	Subcutaneous implant ⇓ Madeup of sialistic rods (non-biodegradable)	1 year
Capronor • Levonorgestrel	Subcutaneous bio-degradable implant	1 year

Side effects of parenteral contraceptive

- Irregular/breakthrough bleeding
- Infertility even after stoppage
- Increased risk of osteoporosis as progesterone reduces LH leading to reduced levels of estrogen



Norplant

- 6 silastic rods → Each rod: 36 mg of levonorgestrel
- Inserted in subcutaneous tissue of the arm
- Effective duration: 5 years

Male contraceptives - Not approved

00:57:20

Gossypol

- From cotton seed
- Spermicidal effect
- Side effect: Hypokalemia

Nonoxynol-9

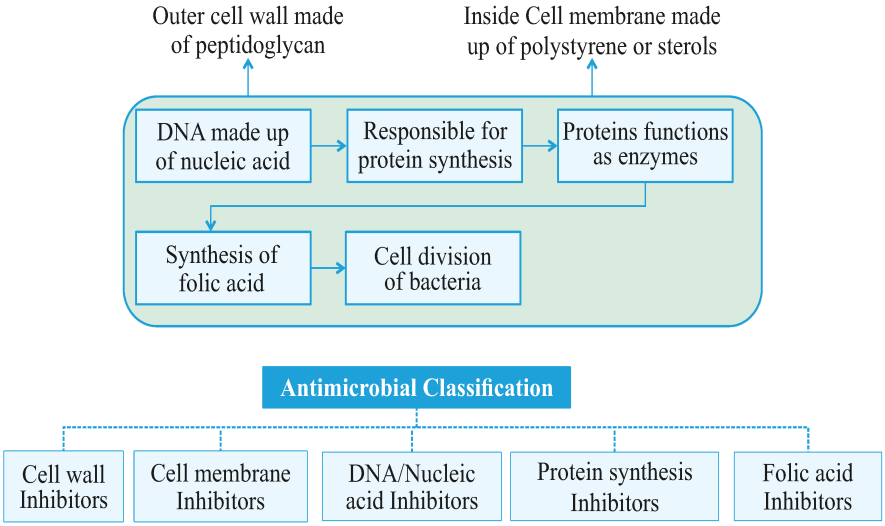
- Spermicidal effect

8 CELL WALL AND CELL MEMBRANE SYNTHESIS INHIBITORS PART-1

- Antimicrobials are drugs against any microbes: Bacteria, Protozoa, Viruses, Fungi, etc.,
- Antibiotics are drugs obtained from a natural source
- All antibiotics are antimicrobials but all antimicrobials are not antibiotics.

Structure of bacteria

00:01:08

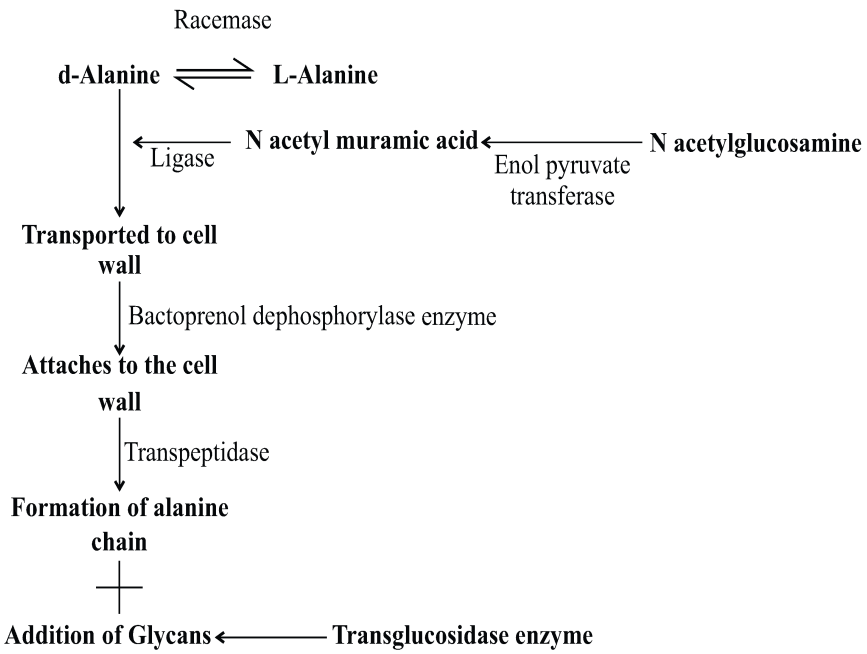


Cell wall Synthesis Inhibitors

00:03:10

- The outer cell wall of the bacteria is made up of peptidoglycan
- Peptidoglycan chains: Peptide chains that are made of amino acid called Alanine and linked with among each other with sugars or glycans

Synthesis



- **Drugs**

B	• Beta lactam group: Penicillin, Cephalosporins, Carbapenems and Monobactam • MOA: Inhibits transpeptidase enzyme
B	Bacitracin
C	Cycloserine
Getting	• Glycopeptide group: Vancomycin • Inhibition of transglucosidase enzyme
Famous	Fosfomycin

  - These drugs are not effective in the treatment of atypical bacteria (Mycoplasma, Chlamydia, Rickettsia) as they lack cell wall
  - All are bactericidal drugs except Cycloserine (Bacteriostatic)

Bacitracin	• MOA: Inhibits bactoprenol de phosphorylase enzyme
	• Obtained from Bacillus subtilis
	• Used as Topical cream in gram-positive cocci skin infection
	  - Staphylococcus infection
	  - Streptococcus infection
	• Less effective against MRSA stain
	• Never given in IV route as it is a nephrotoxic drug

Cycloserine	• MOA: Inhibits alanine racemase and ligase
	• Oral drug for multidrug resistant TB
	• Bacteriostatic agent
	• Side effects: Highly neurotoxic drug
	  - Psychosis
	  - Depression: Increased risk for suicides

Fosfomycin	• Inhibits enol pyruvate transferase • Treats UTI infection due to Foley's catheter- Enterococcal UTI • Dose: 3 gms/oral once

Beta lactam group

00:17:25

Beta lactam group of antibiotics

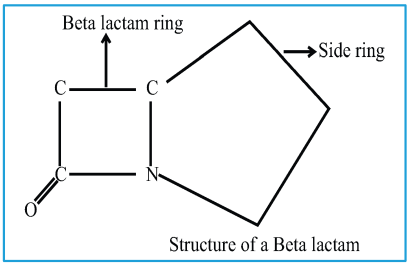
- Penicillin
- Cephalosporin
- Carbapenems
- Monobactam

Mechanism of action

- Inhibits transpeptidase enzyme thereby reducing cell wall synthesis
- Bactericidal drugs

Structure

- Contains beta lactam ring and a side ring depending on the group of drug
- Beta lactam ring inhibits transpeptidase enzyme
- The side ring decides the spectrum of activity and also governs their main side effect
  - Hypersensitivity
  - Cross hypersensitivity
- Monobactam (E.g. Aztreonam) has no side ring and does not show cross hypersensitivity.
- Cephalosporins and carbapenems are avoided in patients allergic or hypersensitive to penicillin, instead monobactams are used



Structure of a Beta lactam

Penicillin group 00:24:05

Drugs ends with

- Cillin

History

- First penicillin: Penicillin G
- Discovered by Alexander Flemming
- Other Name: Benzylpenicillin or Crystalline penicillin
- The only natural penicillin discovered from a fungus: Penicillium notatum
- For commercially use, it was made from Penicillium chrysogenum- Made by Chain, Florey

Pharmacokinetics

- ROA: IV
- Poor CNS penetration, but still used in treatment of Meningitis.
- Poor prostate and eye penetration

Uses

S	Syphilis: DOC for neurosyphilis
M	Meningococcal meningitis (now no longer DOC)
A	Actinomycosis
R	Rat bite fever: Streptobacillus, Spirillosis
T	Tetanus
Player	Pasteurella multocida
G	Gas gangrene (Myonecrosis): Clostridium perfringens

A	Anthrax
Y	Yaws
L	Leptospirosis
E	• Every species: Streptococcus, Staphylococcus if sensitive • Acquired resistance against penicillin G

00:30:45

Treatment of Meningococcal Meningitis

Causative organism • Neisseria meningitidis	**Treatment** • DOC: IV Ceftriaxone (Third generation cephalosporin)
Prophylactic drug • Ciprofloxacin (earlier Rifampicin) • Prevents nasal colonisation	**Prophylaxis in children and in pregnant women** • Injections of Ceftriaxone

Penicillin hypersensitivity 00:34:00

Incidence

- 4-5%

Allergic testing

- Allergen testing with 6 aminopenicillanic acid (side ring in penicillin G)
- Given in intradermal route

Types of hypersensitivity

- **Type 1**: Sudden death due to anaphylaxis (Urticaria, rash)
- **Type 2**: Hemolytic Anaemia- Detected through Coombs test
- **Type 3**: Serum sickness
- **Type 4**: Delayed type of hypersensitivity

Treatment

- DOC: Macrolides (Erythromycin, Azithromycin), Clindamycin

Drawbacks of penicillin G: Synthetic penicillins used to overcome drawbacks of penicillin G

- **Acid labile**: Acid stable penicillins or acid resistant penicillins
- **Short acting**: Long acting penicillins
- **Narrow spectrum**: Extended spectrum penicillin
- **Acquired resistance**: Penicillinase resistant penicillin
  - Beta lactamase inhibitors

Drawbacks of Penicillin G 00:40:00

Acid labile penicillin	Acid stable penicillin

• Oral penicillin G is degraded in the stomach by HCl
• Not given orally
• Oral: Given in high doses (If necessary)
	• **ROA:** Oral
	• **Drugs- Mnemonic:** VODCAA
	  ○ Penicillin V: Phenoxy methyl penicillin
	  ○ Oxacillin
	  ○ Dicloxacillin: Flucloxacillin
	  ○ Cloxacillin
	  ○ Ampicillin
	  ○ Amoxicillin
	• All are avoided with food and antacids except Amoxicillin
	  ○ Given 30 mins before food or >2 hrs after food

00:43:30

Short-acting	Long-acting

• OATP transporter in the kidney rapidly excretes penicillin G in urine	• Penicillin G + Probenecid: Inhibits OATP transporter in the kidney
	  ○ ROA: IV
	Givens as IM depot injections/ Repository injection
	• Procaine Penicillin
	• Benzathine penicillin: Longest acting
	  ○ Half-life: 1 month
	• Procaine given IV is Neurotoxic and causes seizures
	• Benzathine penicillin given IV is cardiotoxic

Benzathine penicillin

- Overall longest acting penicillin
- DOC for prophylaxis of Rheumatic fever
  - Dose: 1.2 million IU once a month
- DOC for Syphilis
  - Dose: 2.4 million IU
  - Given in all stages of syphilis except neurosyphilis

Treatment of Syphilis 00:49:50

- Sexually transmitted disease

Primary syphilis	Chancre
Secondary syphilis	Spread in the blood
Early latent syphilis	Dormant for < 1 year
Late latent syphilis	Dormant for > 1 year
Tertiary syphilis	• Activation after 1 year and damages the organs • Damage to heart: Cardiovascular syphilis • Damage to brain: Neurosyphilis

Stage	Treatment
• Primary syphilis • Secondary syphilis • Early latent syphilis	Benzathine penicillin 2.4 million IU IM: One injection PYQ: FMGE 2021
• Late latent syphilis • Tertiary syphilis • Cardiovascular syphilis	Benzathine penicillin 2.4 million IU IM: Once a week for 3 weeks
Neurosyphilis	**Aqueous penicillins** • Penicillin G + Probenecid: IV • Procaine penicillin
Syphilis with penicillin allergy	Doxycycline > Erythromycin
Syphilis in pregnancy	• Penicillin only • Allergy: Penicillin desensitisation

Jarisch herxheimer reaction

- Penicillin hypersensitivity in syphilis
- Type III hypersensitivity reaction
- Treatment
  - Do not stop penicillin
  - Start corticosteroid

00:57:10

Narrow spectrum	Extended spectrum penicillin

• Not effective against Enterobacteriaceae family
• Gram negative: Inherently resistant to Penicillin G
  ○ Shigella
  ○ Pseudomonas
  ○ Salmonella
  ○ Klebsiella
  ○ Proteus
	• Also effective against Enterobacteriaceae
	Divided into three types
	• Aminopenicillin: Ampicillin, Amoxicillin (A2)
	  ○ ROA: Oral, IV
	• Carboxypenicillin: Carbenicillin, Ticarcillin (CT)
	  ○ ROA: IV
	• Ureidopenicillin: Mezlocillin, Azlocillin, Piperacillin (MAP)
	  ○ Has the largest spectrum
	  ○ Active against Proteus, Anaerobes
	  ○ ROA: IV
	• E Coli: Salmonella, shigella
	  ○ All drugs are effective
	• Pseudomonas: Aminopenicillins are not effective
	• Klebsiella: Ureidopenicillins are effective

Ampicillin	Amoxicillin

• DOC: Listeria meningitis
  ○ Ampicillin + Gentamicin
• DOC: Enterococcus faecalis infection
• More effective against H. Influenza
• Less oral bioavailability
• Excreted in bile
	• DOC: Streptococcus pneumonia
	  ○ ENT infection
	  ○ Community acquired pneumonia
	• More effective against Salmonella typhoid
	• Best oral bioavailability
	• Less excreted in bile

- Overall DOC for H.Influenza, Salmonella typhoid Ceftriaxone
- Ampicillin: Has greater risk of causing diarrhoea
  - Causes Clostridium difficile diarrhoea
  - Other Name: Pseudomembranous colitis
  - Contraindicated: Ebstein barr virus- Causes severe allergy
  - BAC-Ampicillin: Prodrugs of Ampicillin
  - PIV-Ampicillin: Prodrugs of Ampicillin
    → Has better oral absorption

Acquired resistance 01:10:45

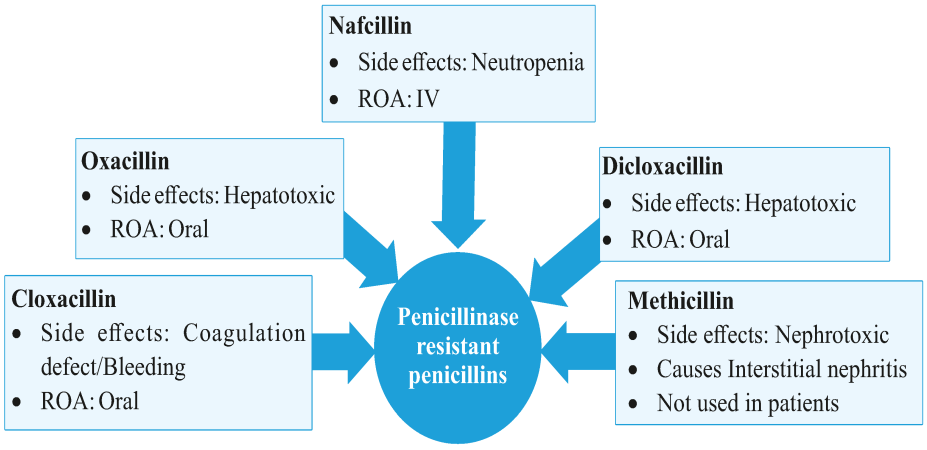
- Penicillinase resistant penicillin
- Beta lactamase inhibitors

Gram positive: Staphylococcus and streptococcus	Gram negative enterobacteriaceae

Penicillin G
↓
Acquired resistance: Penicillinase producing Staphylococcus/Streptococcus
↓
DOC: Penicillinase resistant penicillin
	• Treatment: Extended spectrum penicillins
	  ○ 3rd generation Cephalosporins
	  ○ Acquired resistance: ESBL enzyme
	  → Extended spectrum beta lactamase enzyme
	  ○ Beta lactamase inhibitors: Inhibits ESBL enzyme

Acquired resistance in staphylococcus and streptococcus 01:15:30

- Reason: Production of penicillinase enzyme that degrades penicillin G
- Treatment: Penicillinase resistant penicillin
- **Drugs: Mnemonic** CONDM



01:20:21

MRSA: Methicillin Resistant Staphylococcus aureus

Super bug

- Resistant to many antibiotics

Causes

- Resistance due to the mutation in transpeptidase enzyme
- Other Name: Penicillin binding protein 2A
- Gene abnormality: MEC-2A gene
- Transduction

Resistant to all beta lactam antibiotics

- All penicillins
- All cephalosporins
- All carbapenems
- All monobactams

New drug

- 5th generation cephalosporins
- Effective in MRSA
  - Ceftaroline
  - Ceftobiprole

9 CELL WALL AND CELL MEMBRANE SYNTHESIS INHIBITORS PART-2

Drugs for MRSA (Methicillin-resistant Staphylococcus aureus)

- Divided into three types

IV drugs	• Used in serious infection
	• DOC: Vancomycin (Inhibits transglucosidase enzyme)
	• Vancomycin-resistant Staphylococcus aureus: Linezolid
	• Linezolid resistant Staphylococcus aureus: Streptogramin
	• Streptogramin-resistant Staphylococcus aureus: IV Daptomycin, Tigecycline, 5th generation cephalosporins
	• New drugs
	  ○ IV Iefamulin
	  ○ IV Arbekacin

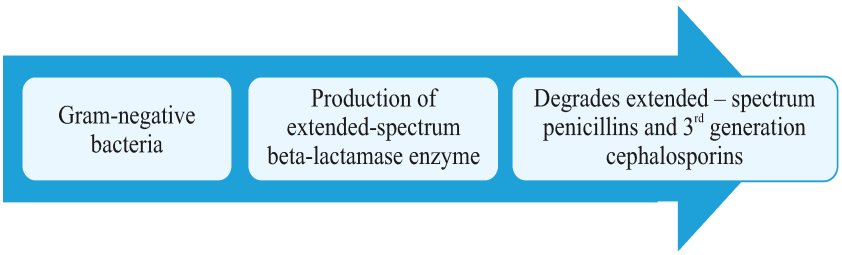
Oral drugs	• Used in non-serious skin and soft tissue infection
	• DOC: Linezolid
	  ○ ROA: Oral and IV
	• Other drugs
	  ○ Clindamycin
	  ○ Rifampicin
	  ○ Cotrimoxazole
	  ○ Tetracycline
	  ○ Fluoroquinolones

Topical creams	• Kills nasal colonization
	• Drugs
	  ○ Mupirocin: 2% ointment
	  ○ Fusidic acid

- Overall DOC for MRSA Vancomycin
- DOC for Vancomycin-resistant Staphylococcus aureus (VRSA): Daptomycin
  - ○ Not available in India
  - ○ Not effective in pneumonia
  - ○ VRSA + Pneumonia: Linezolid
- Drugs not effective in MRSA
  - ○ Beta-lactam antibiotics except 5th generation cephalosporins
  - ○ Macrolides: Erythromycin, Azithromycin

Acquired Resistance in Enterobacteriaceae

00:07:40



- Beta-lactamase Inhibitors: Blocks extended-spectrum beta-lactamase enzyme (ESBL)

Penicillins- 3rd generation cephalosporins	+	Beta-lactamase inhibitors (Irreversibly block ESBL enzyme- Protect)
Amoxicillin Ticarcillin	+	Clavulanic acid
Ampicillin Cefoperazone	+	Sulbactam
Piperacillin Ceftolozane	+	Tazobactam

- Sulbactam has antibacterial activity against Acinetobacter baumannii
- Treatment for EBLS-producing bacteria (E. coli, Pseudomonas, Klebsiella)
  - Extended-spectrum penicillins + beta-lactamase inhibitors
    → 3rd generation cephalosporins + beta-lactamase inhibitors
    → 4th generation cephalosporins: Resistant to ESBL enzyme
    → Carbapenems: Resistant to ESBL enzyme
    → Overall DOC: Carbapenems
- Metallo beta-lactamase enzyme, also known as Carbapenemase
  - Degrades carbapenems and 4th generation cephalosporins
  - DOC: Colistin, Tigecycline
- Carbapenems + beta-lactamase inhibitors: Inhibition of metallo beta-lactamase enzyme

Beta lactams	+	New beta-lactamase inhibitors
Meropenem	+	Vaborbactam
Imipenem	+	Relebactam
Ceftazidime (3rd generation cephalosporins)	+	Avibactam

Cephalosporins

00:19:20

- Divided into 5 generations

<table>
<tr><td>1st generation</td><td>

Best drug for gram-positive infection (E.g. Streptococcus, Staphylococcus)
DOC: Surgical prophylaxis, given<60 mins before surgical incision
Drugs

</td></tr>
<tr><td>2nd generation</td><td>

Better gram-positive compared to 1st generation and less gram-negative activity compared to 3rd generation
Best drugs for anaerobic bacteria (E.g. Bacteroides)
DOC: Metronidazole
Drugs

</td></tr>
<tr><td>3rd generation</td><td>

Best drug for gram-negative bacteria
Recommended for community-acquired gram-negative infections

E. coli, Typhoid, Shigella, Meningococci, Gonococci, H influenza except Pseudomonas

Degraded by ESBL enzyme

</td></tr>
<tr><td></td><td>
<table>
<tr><td>Oral drugs</td><td>Parenteral</td><td>Special anti Pseudomonas: Parenteral</td><td>Two new cephalosporins</td></tr>
<tr><td>• Cefixime
• Cefpodoxime</td><td>• Ceftriaxone
• Cefotaxime</td><td>• Ceftazidime
• Cefoperazone
• Ceftolozane</td><td>• Moxalactam
• Cefiderocol (Siderophore containing cephalosporins)</td></tr>
</table>
</td></tr>
<tr><td>4th generation</td><td>

Nosocomial infection by gram-negative
ROA: Parenteral (IV/IM)
Resistant to ESBL enzyme
Drugs (contains -pi-)

Cefepime
Cefpirome

</td></tr>
<tr><td>5th generation</td><td>

Specifically made for MRSA
It is also effective against VRSA, LRSA, SRSA
Drugs: Parenteral (IV) (drugs contain -rol-)

Ceftaroline
Ceftobiprole

</td></tr>
</table>

Maximum CNS penetration

- Cefuroxime > Cefotaxime (-xime-)

Safe in renal disease

- Cefoperazone > Ceftriaxone (-one-)
- Excreted in bile
- Side effect: Jaundice
- Neonates: Kernicterus

Disulfiram like drugs: Cefoperazone

- Avoid in alcoholism
- Contains MTT ring (Methyl-thio-tetrazole)
- Drugs
  - Cefamandole
  - Cefotetan
  - Cefoxitin

Reduce fibrin levels: Cefoperazone

- Increased risk of bleeding due to Warfarin
- Cefoperazone
  - E: Excess bleeding
  - R: Safe in renal disease
  - A: Alcoholism avoid (Disulfiram)

Cefepime

- Causes encephalopathy

Cephalosporins are not effective against

- **L:** Listeria- DOC: Ampicillin
- **A:** Atypicals- Mycobacteria
- **M:** MRSA-Except 5th generation
- **E:** Enterococcal infections

Uses of Ceftazidime

- DOC: Pseudomonas infection, melioidosis, febrile neutropenia

Carbapenems

00:45:30

Drugs end with -penem-

- Imipenem
- Meropenem
- Doripenem
- Ertapenem: Not effective against Pseudomonas, Acinetobacter
- Faropenem: Oral

Advantage

- These drugs are resistant to degradation of ESBL enzyme

Uses

- Used in nosocomial infections
- DOC:
  - Acinetobacter baumannii (Ventilator-associated pneumonia)
  - Klebsiella
  - Burkholderia
  - Serratia
  - Proteus
  - Pseudomonas

Resistance

- All drugs have acquired resistance against Carbapenems by producing carbapenemases

Side effects

- Nephrotoxic
- Neurotoxic: Seizures
- Maximum toxic: Imipenem
- Imipenem on reaching kidney is converted to toxic form by Dehydropeptidase enzyme (DHP1)
- Imipenem + Cilastatin (DHP1 inhibitor): Reduces toxicity, longer acting

Metallo beta lactamase producing bacteria 00:52:20

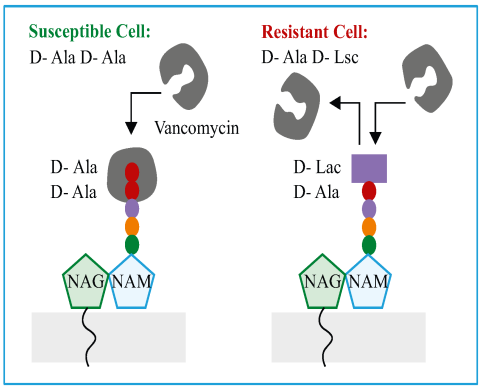
- These bacteria degrade carbapenems
- Bacterias include
  - New delhi metallo beta lactamase (NDM1)
    - → Strain of E coli and Klebsiella
    - → Other names: Delhi Superbug
    - → DOC: Ceftazidime + Avibactam
  - Carbapenem resistant Acinetobacter baumannii (CRAB)
  - Carbepenem resistant Klebsiella pneumoniae (CRKP)
- DOC: Colistin, Tigecycline

Monobactam 00:55:55

- Drug: Aztreonam
  - IV drugs for gram-negative infections: Typhoid, Pseudomonas
  - No cross allergy with Penicillins + Cephalosporins + Carbepenem as it has no side rings
  - Cross allergy with Ceftazidime

Glycopeptides Group 00:57:45

- Inhibits cell wall synthesis by inhibiting the attachment of glycans (Transglucosylase) and binding to d-alanine and d-alanine
- Drugs
  - Vancomycin: Cidal drugs
  - Teicoplanin
  - Oritavancin, Telavancin, Dalbavancin
    - → Other Name: Lipoglycopeptide
    - → Also, inhibits the cell membrane of bacteria and is more effective than vancomycin



- Resistant to vancomycin occurs due to bacteria changing the structure of the cell wall by producing d-Alanine-d-lactose

Spectrum of Vancomycin

- Only effective against gram-positive bacteria
- Recommended against gram-positive resistant cases
- Gram-positive infection resistant to Vancomycin
  - Leuconostoc
  - Pediococcus
  - Erysipelothrix
  - Lactobacillus

Uses of Vancomycin

- Administered intravenously as it is a polar drug, highly water soluble
- DOC: MRSA, MRE (Enterococcus), and Toxic shock syndrome toxins
- Oral vancomycin: Not absorbed from the intestine but it kills local GIT infection
  - DOC: Pseudomembranous colitis caused Clostridium difficile infection
  - DOC: Staphylococcus enterocolitis
- Teicoplanin: IV/IM
  - Causes ototoxicity and nephrotoxicity (Less)

Side effects of Vancomycin

- Ototoxicity
- Nephrotoxicity
- **Red man syndrome**
  - Vancomycin causes histamine release from mast cells leading to Flushing on the face, red color rashes, hypotension
  - This is seen when Fast IV injections of Vancomycin are given
  - Slow infusion is recommended

Toxic Shock Syndrome 01:11:55

- Caused by superantigens of Staphylococcus or Streptococcus bacteria
  - Excessive toxin production leads to multiple organ damage
- Skin becomes scaled
- Treatment
  - Kill bacteria: IV Vancomycin
  - Reduce toxin production: Clindamycin

Important Information

- Infections producing toxins
  - Tetanus
  - Botulinism
  - Gas gangrene
  - Toxic shock syndrome

Clostridium difficile diarrhea (CDI)

01:14:50

- Causes: Pseudomembranous colitis
- Other Name: Antibiotic-associated diarrhea

- Antibiotics causing Clostridium difficile
  - Clindamycin (Highest risk)
  - 3rd generation cephalosporins
  - Ampicillin
  - Fluoroquinolones

Treatment

Very	• Oral Vancomycin • DOC in India
Famous	• Fidaxomicin-Macrolide antibiotic • DOC in America • Most effective
Business	• Bezlotoxumab: Monoclonal antibody against toxin B
Make	• Metronidazole: Mild diarrhea
Rich	• Rifaximin
Fortune	• Fecal microbiota transplant • Other Name: Stool transplant • Replace the good bacteria

First CDI episode	• Start oral Fidaxomicin > Vancomycin • Duration: 10 days
First recurrence	• Start oral Fidaxomicin > Vancomycin • Duration: 20 days
Second recurrence	• Start oral Fidaxomicin > Vancomycin + Rifaximin, Fecal microbiota transplant
Fulminant CDI	• Causes shock, hypotension, paralytic ileus • Oral vancomycin + IV Metronidazole • To Block toxin production: Bezlotoxumab

Cell Membrane Inhibitors

01:24:10

- Divided into two groups

Lipopeptide	• Drug: Daptomycin • MOA ○ Detergent-like action- Causes depolarisation of cell membrane leading to death of the cell • Bactericidal drugs • Used as an IV drug for resistant gram-positive infection • DOC: Vancomycin-resistant (VRSA, VRE)

Polypeptide	• Drugs
	  ○ Polymyxin B
	  ○ Polymyxin E: Colistin
	  → IV: Colistimathe
	• Used as topical, IV, aerosols (Pneumonia)
	• Bactericidal drugs
	• Resistant gram-negative infections
	  ○ Resistant to Carbapenems
	  ○ Eg: Delhi superbug, CRAB

- Daptomycin
  - It is not effective in pneumonia as the surfactant of the lungs inactivates Daptomycin
  - Side effects
    - → Muscle pain (Myalgia)
    - → Joint pain (Arthralgia)
- Colistin
  - Carbapenem resistance cases: E coli, Klebsiella, Pseudomonas, Acinetobacter
  - Not effective in
    - → Burkholderia
    - → Serratia
    - → Proteus
  - Side effects
    - → Nephrotoxicity
    - → Neurotoxicity

10 DNA/NUCLEIC ACID INHIBITORS

	DNA Damagers/Disruptors	DNA Gyrase/Topoisomerase 4 inhibitor
MOA	They produce nitric oxide, which causes DNA damage	Inhibit replication of DNA
Drugs	• Nitroimidazole (metronidazole) • Nitrofurantoin	• Fluoroquinalones (-floxacin) • Novobiocin→used in microbiology lab as a diagnostic test

- Nitroimidazole and Fluorquinalones are cidal drugs
- Nitrofurantoin and Novobiocin are static drugs

Novobiocin Test

- When put on an agar plate, novobiocin
  - Kills →staphylococcus saphrophyticus
  - Does not kill → staphylococcus epidermidis

Nitroimidazole

00:04:30

Drugs (end with - nidazole)

- Metronidazole
- Ornidazole
- Tinidazole
- Satranidazole
- Secnidazole ← longest acting drug

Mechanism of action

- Inside the bacteria, they produce Nitric oxide free radicals
  1. Cause DNA damage
  2. Inhibit PFOR enzyme (pyruvate ferritin oxido reductase) and causes DNA damage

Resistances

- Bacteria create Nim-reductase that inactivates the free radicals of nitric oxide

Uses of Metronidazole

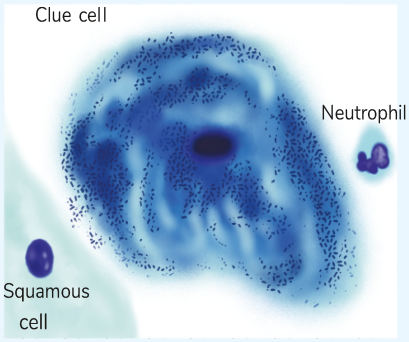
- Anaerobic bacteria (ineffective in aerobic bacteria → oxygen)
  - E.g. bacteroids
- Protozoan / flagellates → inhibits PFOR enzyme

Metronidazole is Drug of choice for

- **G**iardiasasis → Diarrhea in HIV- positive patients
- **E**ntamoeba histolytica → Amebic dysentery & amebic liver abscess
- **T**richomonas vaginalis
- **D**racunculus (guinea worm)
- **G**ardenella / bacterial vaginosis
- **A**naerobic bacteria
- **P**seudo membranous colitis
- **P**eptic ulcer due to H.pylori

Guess the disease

Bacterial vagionsis



Presence of Clue cell indicated
Bacterial vaginosis

Trichomonas vaginalis

A female presents with abnormal yellow-green vaginal discharge and an unpleasant fishy smell. On examination, "Strawberry cervix" with punctuate hemorrhages is noted.
Ans. Trichomonas vaginalis → since it is an STD. both partners must be treated

Side effects of Nitroimidazole (metronidazole)

- Metallic taste
- Diarrhea
- Brown color urine
- Metronidazole-like drugs cause disulfiram reaction must be avoided in alcoholics as they cause dangerous side effects

Metronidazole in pregnancy

- It must be avoided in the first trimester but can be given safely in the second and third trimesters because organogenesis in a fetus happens in the first trimester

Other Nitroimidazoles

- Benznidazole → DOC for Chagas disease (Trypanosoma)
- Nifurtimox → DOC for Chagas disease (Trypanosoma)
- Nitazoxanide → DOC for Cryptosporidium parvum
  - Metronidazole is not effective for the above diseases
  - MOA for the above drugs is the same as metronidazole, they inhibit the PFOR enzyme

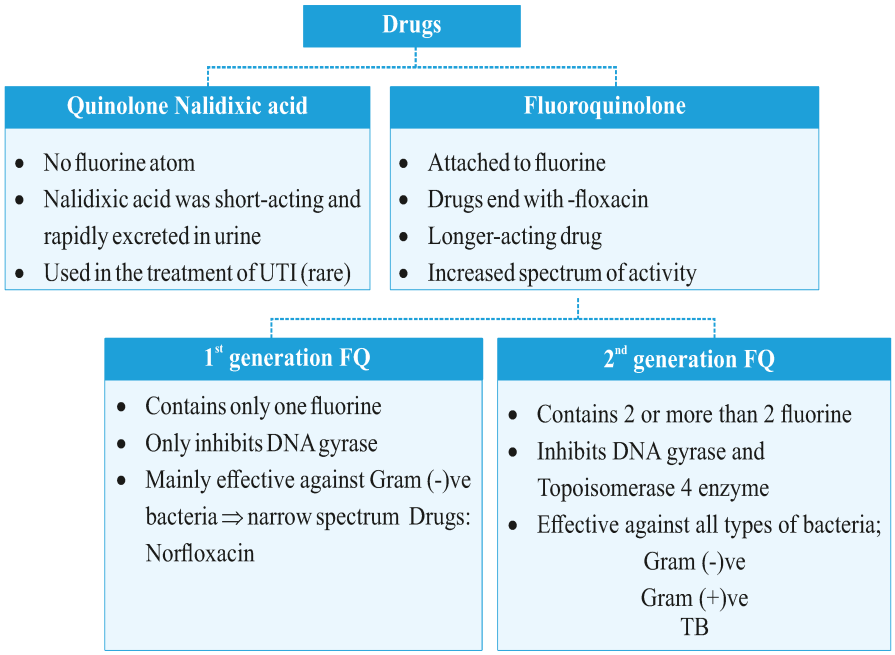
Newer drugs

- Delamanid and Pretomanid are new drugs developed for the treatment of MDR-TB (multidrug-resistant - tuberculosis)

Fluoroquinolones

00:16:25

- **Mechanism of action**
  - Inhibits DNA Gyrase
  - Inhibits Topoisomerase 4 enzyme (only by 2nd generation fluoroquinolones)
  - Two strands of DNA divide and a complementary strand of DNA is synthesized. These strands must be separated for the division of the cell. The negative coiling is maintained by the DNA gyrase/ Topoisomerase 4 enzyme. Inhibiting these enzymes prevents DNA replication
- **Resistance to FQ**
  - Mutation in DNA gyrase enzyme



Norfloxacin	• Used for treatment of chronic UTI/ diarrhea • DOC for spontaneous bacterial peritonitis
Ciprofloxacin	• Drug of choice for ○ Pseudomonas ○ Anthrax ○ Pyelonephritis (UTI) ○ Typhoid, Traveler's diarrhea ○ Meningococcal prophylaxis • Disadvantages ○ CYP enzyme inhibitor →Toxicity of other drugs (Theophylline /Warfarin)in the body increases → Increased chances of seizure and bleeding
Levofloxacin	• Levofloxacin does not inhibit CYP enzyme • Effective for ○ Pseudomonas ○ Anthrax ○ Plague prophylaxis
Respiratory FQ	• FQ is used for Community-acquired pneumonia ○ Levofloxacin ○ Gatifloxacin ○ Gemifloaxicin ○ Moxifloxacin
FQ in TB	• FQ used in MDR TB ○ Levofloxacin ○ Moxifloxacin →most effective in TB

Longest acting FQ

- Sparfloxacin > Moxyfloaxicin

FQ with maximum oral absorption

- Levofloxacin : 100% oral absorption
- In addition to,
  - Not a CYP inhibitor
  - Easily combined with other drugs

Max CNS penetration

- Pefloxacin

FQ safe for renal failure

- Not excreted in urine. Instead, they are excreted in bile
- Safe drugs for renal failure are,
  - Pefloxacin
  - Moxifloxacin
  - Trovafloxacin (banned due to hepatotoxicity)
- Not used in UTI treatment
- These are contraindicated in
  - Hepatic disease
  - Liver disease

New drugs

- Delafloxacin is a new drug that is the most effective FQ for MRSA
- Non- fluorinated quinolones
  - Ozenoxacin
  - Neonoxacin

Adverse effects of FQ

Heart	Hypoglycemia → insulin release

ECG	• Epilepsy
	  ○ Seizure (blocks GABA receptors in the brain)
	  ○ Higher risk when combined with FQ + theophylline / NSAID

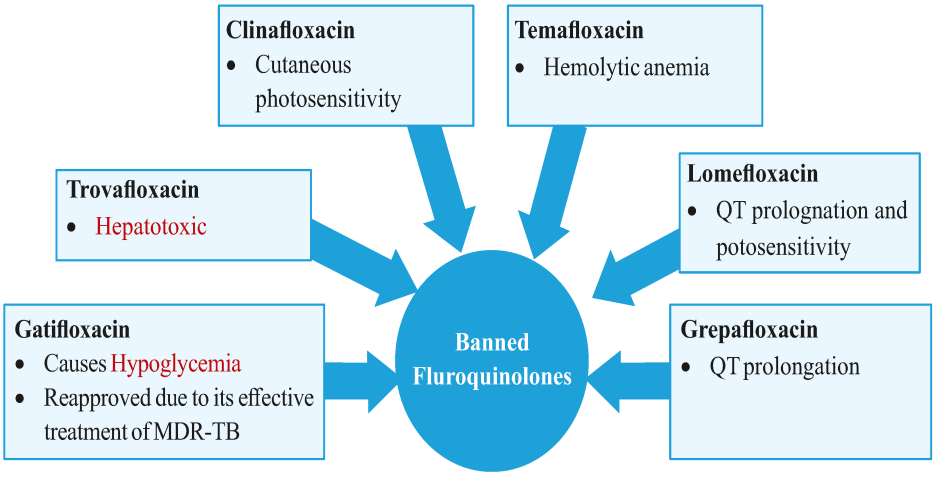
P	• Photosensitivity (if given as a topical cream) • FQ and tetracycline are never given as creams
Q	QT prolongation → block potassium channel in the heart
R	Rashes
S	Superinfection of Clostridium difficile
T	Tendinitis → Achilles tendon rapture in old age patients

Important Information

- Max QT prolongation- Sparfloxacin > Moxiflxacin>Grepafloxacin
- Least QT prolongation- Ciprofloxacin

Contraindications

- FQ (and tetracycline) must be avoided during,
  - Pregnancy
  - Patients <18 years
- As they can lead to bone and cartilage defect



Urinary Antiseptics 00:41:40

- Used to treat lower UTI (infection of the Ureter, bladder, and urethra)
- Given orally and rapidly excreted into urine and kill infection in the bladder
- Nitrofurantoin is contraindicated in renal failure

Urinary antiseptics

Acidic urine	Alkaline Urine	pH irrelevant
• Nitrofurantoin • Methenamine mandelate • Tetracycline	• Cotrimoxazole • Cephalosporins • Aminoglycoside • FQ (norfloxacin)	• Chloramphenicol • Amoxicillin / Ampicillin

- Nitrofurantoin is ineffective for proteus-UTI as it turns urine alkaline

Overall DOC for UTI

- Mild UTI →Cotrimoxazole
- Severe/ Hospital acquired → β Lactams (amoxicillin) + β Lactamase inhibitor

UTI in Pregnancy

- DOC: Amoxicillin/Ampicillin
- Nitrofurantoin (avoid during the first trimester)

00:48:15

Nitrofurantoin

MOA
- Produces nitric oxide leading to DNA damage

Uses
- Used in the treatment of lower UTIs caused by E.Coli
- Not effective in proteus

Side effects
- Brown urine

Contraindication
- G6PD deficiency (increased chances of hemolysis in RBC)

Methenamine mandelate/ Hippurate
- Effective in acidic urine
- Forms formic acid that kills bacteria
- Add vitamin C

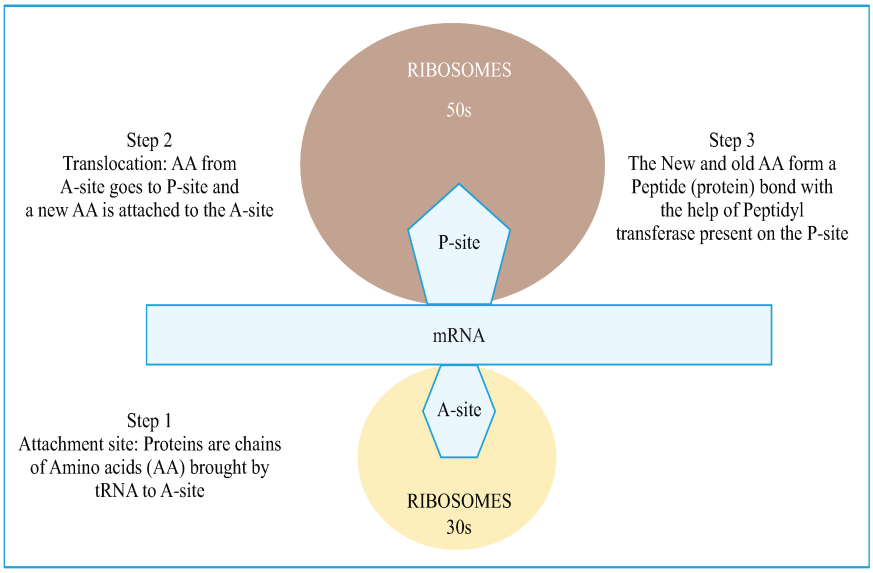
Phenazopyridine
- NSAID
- Also known as Urinary analgesic
- Given for the treatment of dysuria

Cranberry juice
- Effective against UTI due to E. Coli: Causes detachment of fimbria from the urinary tract, causing E. Coli to get washed out into the urine

11 PROTEIN SYNTHESIS INHIBITORS

- Protein synthesis occurs due to the translation of mRNA
- Protein synthesis inhibitors inhibit the translation of mRNA in the bacteria

Translation of mRNA in bacteria



Mechanism of actions of Protein synthesis inhibitors

00:03:15

Inhibit attachment	• Tetracycline, Tigecycline • Block A-site on 30s Ribosomes • Inhibits tRNA AA attachment to A-site
Inhibit translocation	• Macrolides: Erythromycin, Azithromycin • Clindamycin • Streptogramin: Quinpristine + Dalfopristin (30:70)
Inhibit peptide bond	• Inhibits Peptidyl transferase by attaching on 50s ribosome • Chloramphenicol
Inhibit initiation of protein synthesis	• Linezolid • Attaches to 23s subunit present on the 50s ribosome • Inhibits attachment of Methionine tRNA (Methininie is the first AA to initiate protein synthesis)
Multiple mechanisms	• Aminoglycoside • Binds to 30s • Inhibits initiation of protein synthesis • Misreading of mRNA- Defective AA attaches • Inhibit polysome formation (Attachment of ribosomes on mRNA)

Drugs acting on 30s ribosomes
- Aminoglycoside
- Tetracycline
- Tigecycline

Drugs inhibiting the initiation of protein synthesis
- Linezolid
- Aminoglycoside

Drugs acting on 50s ribosomes
- Macrolides
- Clindamycin
- Streptogramin
- Chloramphenicol
- Linezolid
- Quinpristine/ Dalfopristine

Drugs acting 23s subunit on 50s ribosomes specifically
- Linezolid

Bactericidal drugs
- Aminoglycoside
- Streptogramin

Bacteriostatic drugs
- Remaining

Spectrum of the drugs

00:11:05

Broad spectrum	Intermediate spectrum	Narrow spectrum
Against all types of bacteria	Middle	Few bacteria
Drugs • Chloramphenicol • Tetracycline • Clindamycin • Tigecycline	Macrolides • Erythromycin • Azithromycin	Drugs • Aminoglycoside ○ Gram -ve aerobic • Linezolid ○ Gram +ve • Streptogramin ○ Gram +ve

Chloramphenicol

00:13:00

Resistance
- Enzymatic inactivation by bacteria
- CAT (Chloramphenicol AcetylTransferase) enzyme
- In past, Chloramphenicol was the DOC: Typhoid
- Now used rarely due to widespread resistance

Properties
- Oral and IV drug
- Broad spectrum
- BBB penetration is high
- Can be given in empirical treatment of meningitis

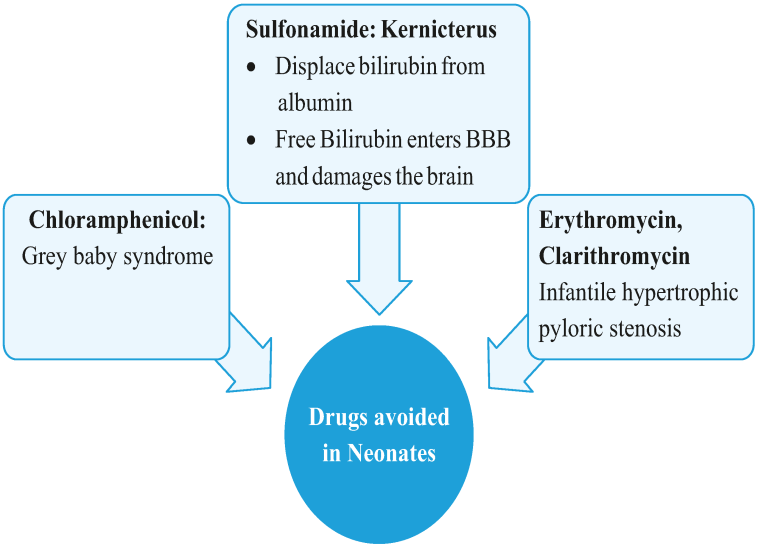
Properties

Bone marrow suppression	Babies

• Aplastic anemia
• Drug is rarely used
• Dose-dependent (Toxicity)
  ○ Reversible by dose reduction
• Dose independent
  ○ Irreversible/permanent
  ○ Idiosyncratic reaction
  ○ Bone marrow transplantation
	• Grey baby syndrome
	• Contraindicated in Neonates

Metabolism

- Chloramphenicol is metabolized by CYP3A4 + UDP-GT in liver
  - Inhibition of CYP3A4 + UDP-GT in liver reduces drug degradation/ metabolism leading to toxicity
  - In high doses, it inhibits mitochondria leading to cell death
  - In neonates, this causes Grey baby syndrome: The skin becomes grey



Tetracyclines

00:22:10

- **Resistance**
  - Effluxed out of bacteria by an abnormal transporter called P-glycoprotein
- **Tetracyclines and their uses**

Group 1 **(Old drugs)**	Tetracycline • DOC: Prophylaxis of cholera • Treatment of Peptic ulcer (H. Pylori) Chlortetracycline Oxytetracycline

<table>
<tr><td>Group 2</td><td>Demeclocycline
Not commonly used
Blocks ADH receptor on kidney
Treatment of SIADH (Syndrome of inappropriate ADH secretion)
Side effects: Nephrogenic Diabetes insipidus</td></tr>
<tr><td>Group 3</td><td>Minocycline
Treatment of Leprosy and Acne (orally)
Doxycycline
Longest-acting drug in this group
Safe in renal disease/failure
The most potent and least dose required
DOC for :
<table>
<tr><td>Less</td><td>• Leptospirosis
○ Treatment and prevention</td></tr>
<tr><td>R</td><td>• Rickettsial infection
○ Atypical bacteria
○ Act on All species</td></tr>
<tr><td>B</td><td>Borrelia</td></tr>
<tr><td>C</td><td>Chlamydia, Cholera</td></tr>
<tr><td>In</td><td>Injected into pleura</td></tr>
<tr><td>Blood</td><td>Brucellosis</td></tr>
<tr><td>Produce</td><td>Plague prophylaxis</td></tr>
<tr><td>Microcytic</td><td>Mycoplasma hominis</td></tr>
<tr><td>Anemia</td><td>Anthrax</td></tr>
</table>
</td></tr>
</table>

- Doxycycline causes fibrosis of the pleura membrane causing Pleurodesis (both pleura adhere to each other)
  - Treatment of pneumothorax- Doxycycline, Talc
- Streptomycin is used in treating plague
- Azithromycin is not effective in Mycoplasma hominis
  - Effective in Mycoplasma pneumoniae

Important Information

- Treatment of Peptic ulcer (H. Pylori)
- Quadruple regimen (CAT)
  - Clarithromycin
  - Amoxicillin
  - Tetracycline

- **Interaction of Tetracycline and calcium**
  - Calcium is present in bones and cartilage in the body
  - Tetracyclines chelate with calcium due to their structure
  - Avoid Tetracycline with milk-containing food
    → Curd, ghee, milk
  - Decrease absorption of both tetracycline and calcium

- **Contraindications**

Children <8 years of age
- Stunting
- Mottling: Damage

Pregnancy
- Bone and cartilage defects in a fetus

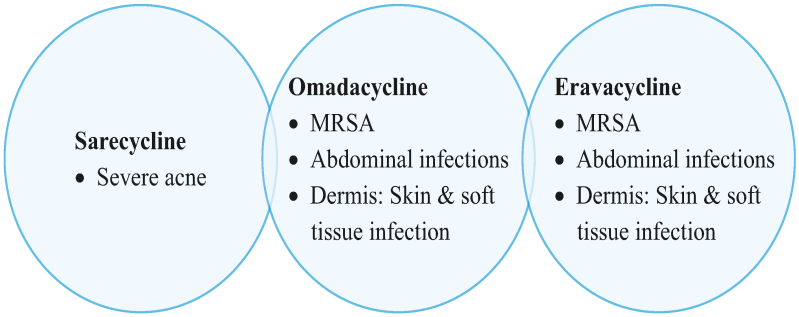
Mottling of teeth

- **Adverse effects**

Very	• Vestibulotoxic/ear damage- permanent • Minocycline
R	• Renal failure • All are contraindicated except doxycycline
A	• Anti anabolic effect • Stunted growth
P	• Photosensitivity - skin damage • Contraindicated as topical skin creams
I	• Increase ICP • Pseudotumor cerebri
D	• Diabetes insipidus (Demeclocycline) • Block ADH receptors on kidney
L	• Liver failure • All are contraindicated
F	• Fanconi syndrome • PCT in nephron is damaged • Expired tetracycline
T	• Tooth damage/discoloration • Chelate with Tetracycline

Important Information
- Drugs contraindicated as topical skin creams are
  - Tetracycline
  - Fluoroquinolones
- Drugs causing Pseudotumor cerebri
  - vitamin A
  - OCP
  - Tetracycline

- **Newer Tetracyclines**



Tigecycline

00:38:55

- Same uses as Omadacycline
- Not kept under tetracycline as it is structurally different.
- **Group:** Glycyl-cycline
- **Properties**
  - IV drug
  - Renal safe drug
  - Reserve drug
    - → Resistance is uncommon but developing
    - → Rarely effluxed by P-glycoprotein
    - → For Hospital-acquired infections
    - → Also used in Acinetobacter baumannii infections causing Ventilator-associated pneumonia

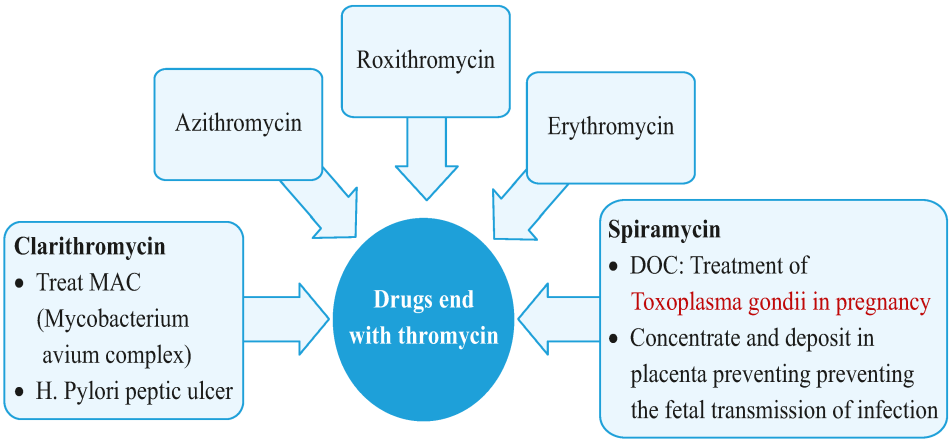
00:42:10

Treatment of Borrelia	Treatment of Leptospirosis treatment
• Borrelia burgdorferi ○ Relapsing fever ○ DOC: Doxycycline ○ In meningitis: Add Penicillin G /Amoxicillin • Borrelia recurrentis ○ Lyme's disease	• DOC: Doxycycline ○ Treatment and prevention • Meningitis: Add 3rd generation cephalosporins ○ Ceftriaxone

Macrolides

00:44:05

- **Resistance**
  - Mutation in 50s ribosomes



  - Most preferred: Azithromycin > Clarithromycin in treating MAC infections and H.pylori

- **Properties**

Pharmacokinetics	Erythromycin	Clarithromycin	Azithromycin
Duration	Shortest acting (3-4 times a day)	→→→→→→→	Longest acting, OD
CYP/p-glycoprotein inhibiting action	Maximum	→→→→→→→	Least, safe
QT prolongation	Maximum	→→→→→→→	Least, safest

- **Advantages** of macrolides over tetracyclines
  - Do not chelate with calcium
    → Safe in children (<8 years), pregnancy- Azithromycin

Important Information

- Doxycycline is used for treating Cholera but Azithromycin is used in Cholera during pregnancy

- **Uses of macrolides (Azithromycin, Erythromycin), DOC in:**

C	Community-acquired pneumonia
C	Cholera in pregnancy and children
C	• Chancroid • STD: Haemophilus ducreyi
C	Corynebacterium diphtheriae
C	Cammylobacterium donovanosis (STD)
S	STDs
L	Legionella pneumonia
A	Atypical pneumonia: Mycoplasma pneumoniae
B	Bordetella pertussis: Whooping cough, Pneumonia

- **Adverse effects**

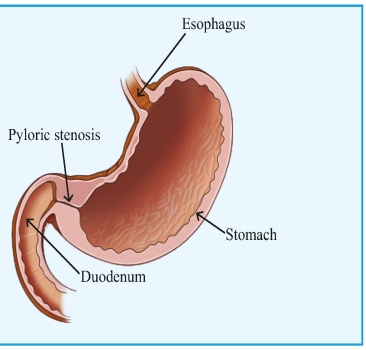
M	• Motilin receptors stimulation in GIT ○ Contract: Diarrhea, hypertrophic pyloric stenosis ○ Max risk: Erythromycin, Clarithromycin ○ Not seen with Azithromycin
A	Allergy
C	Cholestatic jaundice
RO	Reversible Ototoxicity (Stop the drug)
I	Immunomodulatory effects (Decrease CMI) by inhibiting calcineurin enzyme in T-lymphocyte
Q	QT prolongation

Important Information

- Erythromycin is given as a treatment for gastroparesis in Diabetes Mellitus
  - Maximum contraction

- **Contraindications**

- In Neonates, can cause Hypertrophic pyloric stenosis
  - Erythromycin, Clarithromycin
  - Safe: Azithromycin



- **Newer macrolides**
  - Tacrolimus
    - → Used as an immunomodulator in organ transplantation
    - → Inhibits calcineurin enzyme
  - Telithromycin, Solithromycin
    - → Ketolide antibiotics
    - → Action similar to macrolide
    - → Structure is different

Treatment of STDs Medicine 00:58:35

Neisseria gonorrhoea (Gram-negative)	Chlamydia
• Inj. Ceftriaxone 500 mg IM OD + Azithromycin 2 g oral OD • Doxycycline is not effective • If a person is allergic to ceftriaxone Spectinomycin or Gentamicin (Aminoglycosides) is given	• Lymphogranuloma venereum • Ceftriaxone is not effective as Chlamydia has no cell wall • Inj. Doxycycline 100 mg oral BD for 5 days + Azithromycin 1g oral OD

Treatment of Diptheria

- Caused by toxins of Corynebacterium diphtheriae
- DOC: Erythromycin or Azithromycin > Penicillin V
- In resistant cases, Rifampicin is given
- Diphtheria Antitoxin should also be given

Treatment of Pertussis

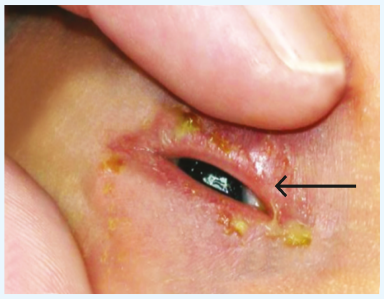
- Whooping cough: Bordetella pertussis
- Macrolides
  - Erythromycin
  - Clarithromycin
  - Azithromycin: Safest in neonates
- Cotrimoxazole

Important Information

- Azithromycin is effective in both Gonococcal and chlamydial infections and 2 g is given in mixed infections
- Erythromycin and clarithromycin cause Infantile hypertrophic pyloric stenosis, and cotrimoxazole causes kernicterus in neonates

- **Prophylaxis of Neonatal conjunctivitis**

- Passing through the genital tract of the mother, bacteria can infect the eyes of neonates
- Ophthalmia neonatorum
- Eye drops prophylactically
  - Silver nitrate (1%)
  - Erythromycin (0.5%)
  - Tetracycline (1%)



Ophthalmia neonatorum

Lincosamides

01:06:20

- Drugs: Clindamycin, Lincomycin
- **MOA**
  - Binds to 50s ribosomes
  - Inhibit translocation similar to macrolides
  - Cross resistance with macrolides
  - Broad spectrum
- **Uses**
  - Treatment of anaerobic bacteria
    - → Prevotella
    - → Acne: Propionibacterium acnes
  - Reduce toxin production
    - → Toxic shock syndrome: Add Vancomycin, which kills bacteria
    - → Tetanus, Botulinum: Add Penicillin G, kills bacteria
  - Protozoal infections
    - → Pneumocystis, not DOC
    - → Malaria
    - → Toxoplasma
- **Side effects**
  - Hepatotoxic
  - Pseudomembranous colitis, Highest risk
    - → Clostridium difficile bacteria

Anaerobic bacterial infections

Supradiaphragmatic infections
- Most common: Prevotella
- DOC: Clindamycin

Infra diaphragmatic infections
- Most common: Bacteroides
- DOC: Metronidazole

Linezolid

01:12:25

Group

- Oxazolidinones

New drugs

- Tedizolid
- Sutezolid

Narrow spectrum drug

- Gram positive resistant bacteria
  - Staphylococcus aureus: MRSA, VRSA
  - Enterococci: MRE, VRE
  - MDR-TB

Properties

- Orally (100% BA) and IV
- Safe in renal failure

Side effects: COMB

- Chorioretinitis: Blindness
- Optic neuritis: Blindness
- MAO (Monoamine oxidase) inhibitor: Serotonin syndrome
- Bone marrow suppression (monitor platelet count)

Streptogramin

01:18:00

- Mixture of Quinpristine + Dalfopristine (30:70)
- Bactericidal combination
- Narrow spectrum used against Gram (+)ve resistant bacteria
  - Even effective in linezolid-resistant bacteria
  - MRSA, VRSA, LRSA
- Given intravenously
- **Side effects**
  - Myalgia
  - Arthralgia

Aminoglycoside

01:19:35

Resistance

- Enzymatic inactivation: Degradation of aminoglycoside
- Except: Amikacin, Plazomicin (Most effective)

Properties

- Highly polar drugs
- Water soluble
  - Do not cross cell membrane and not absorbed orally
  - Used as IV or IM in systemic infections

Metabolism

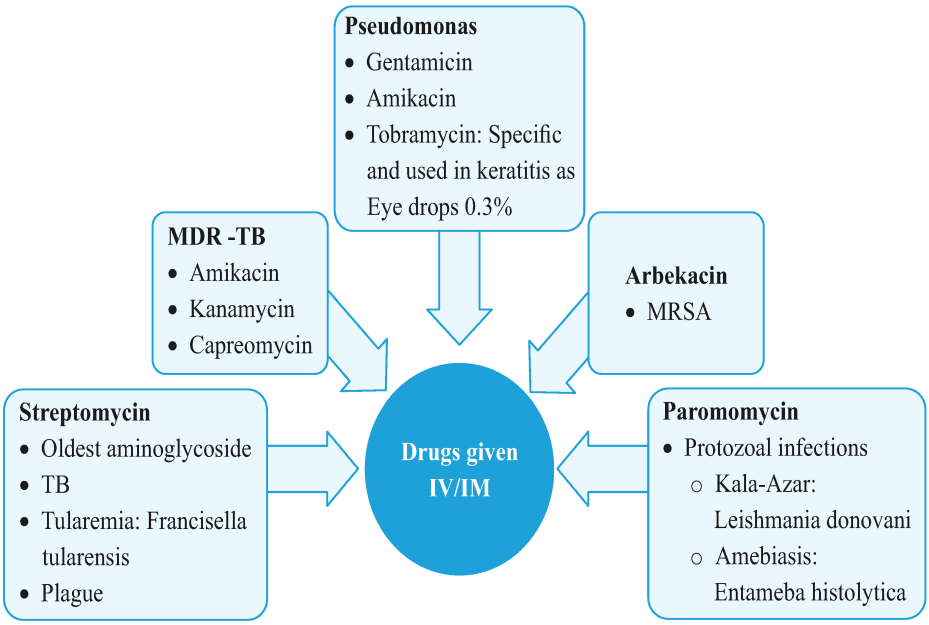
- Not metabolized in liver and are excreted unchanged in urine by glomerular filtration
- Safe in liver diseases
- Require dose reduction in renal disease and old age patients as GFR is reduced

Contraindications

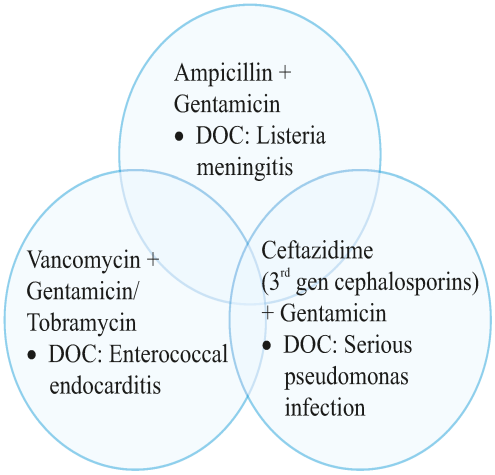
- Contraindicated in pregnancy as it can cause Fetal ototoxicity

Spectrum

- Narrow spectrum drug
- Only effective against Gram (-)ve aerobic bacteria
- Require oxygen dependent porin transporter that is not present in anaerobic bacteria
- Not effective in Burkholderia, Anerobes, Typhoid, Acinobacter boumanii



- Synergistic (additive) effect
  - Combined with Cell wall inhibitors aminoglycoside enters the cell very easily and inhibits protein synthesis
  - Combinations



- **Routes of aminoglycoside**

Inhaled aminoglycoside (aerosols)	• Enter lungs • Amikacin, tobramycin • Treatment of Pneumonia ○ Pseudomonas causes lung damage in cystic fibrosis
Oral aminoglycoside	• Gut sterilization: Not absorbed orally → kill local GIT bacteria • Used in liver failure ○ In hepatic encephalopathy, ammonia is produced and not converted to urea which leads to increased levels of ammonia and brain damage • Oral neomycin • DOC: Rifaximin • Laxative: Lactulose syrup

Topical aminoglycoside creams	• Framycetin
	  ○ Brand: Soframycin
	• Neomycin
	  ○ Brand: Neosporin
	  ○ Overall toxic
	• Both are never given by injections as they are not absorbed orally
	  ○ Most toxic

Anaerobic bacterial infections

Ototoxicity
- Damage hair cells (Neurons projecting into endolymph)
- Irreversible: Epithelial cells do not regenerate
- Cochlear damage leads to high frequency hearing loss
- Vestibular damage leads to imbalance, ataxia, vertigo

Nephrotoxicity
- Damage tubular cells of nephron (PCT, DCT) leads to renal tubular acidosis
- Reversible: Epithelial cells regenerate

N-M blockage
- Neurons release ACh and act on muscles
- Nm Receptor contracts muscles
- Aminoglycoside inhibit release of ACh and block Nm Receptor leading to muscle paralysis
- Contraindication: Myasthenia gravis

  ○ Antidote for aminoglycoside toxicity: Calcium

	Maximum risk	Least risk
Ototoxicity	Cochlear Toxicity • Kanamycin < Amikacin < Neomycin Vestibulotoxic • Streptomycin- Not given for long periods in TB	Netilmicin
Nephrotoxicity	Neomycin > Gentamicin	Streptomycin
N-M blockage	Neomycin (not used) > Streptomycin	Tobramycin

Treatment of Enterococcal infections

Medicine

01:44:00

Endocarditis in IV drug abusers	Catheter associated UTI

• **Enterococcus faecium**
  ○ DOC: Ampicillin + Gentamicin/Ceftriaxone
  ○ Resistance: Vancomycin + Gentamicin
• **Enterococcus faecalis**
  ○ DOC: Daptomycin/Linezolid + Gentamicin
	• Due to enterococcus
	• Fosfomycin
	  ○ 3g orally single dose

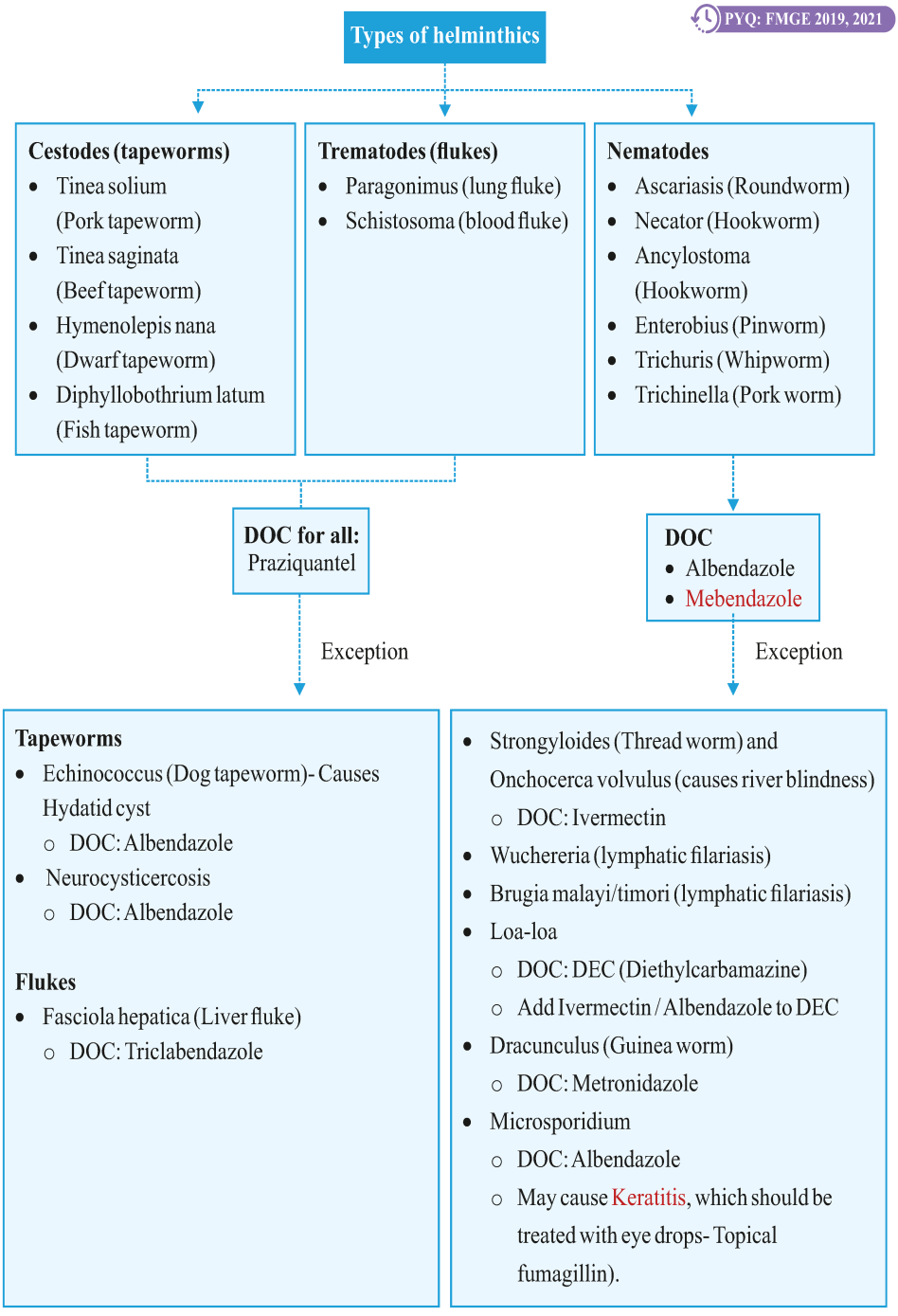
Drugs for pseudomonas

01:46:10

Penicillins	• Carbenicillin, Ticarcillin • Mezlocillin, Azlocillin, Piperacillin (common in India)
Cephalosporins	**3rd generation**: • Ceftazidime • Cefoperazone • Ceftolozane **4th generation**: • Cefepime • Cefpirome **5th generation**: • Ceftobiprole • Ceftaroline
Carbapenems	• Imipenem • Carbapenem
Colistin	Drug of last resort
Aztreonam	Beta lactam antibiotics
Aminoglycoside	• Gentamicin • Amikacin • Tobramycin
Fluoroquinolone	• Levofloxacin, Ciprofloxacin • Only drugs given orally for pseudomonas • All others drugs are injectables

12 ANTI-HELMENTHICS AND SCABIES

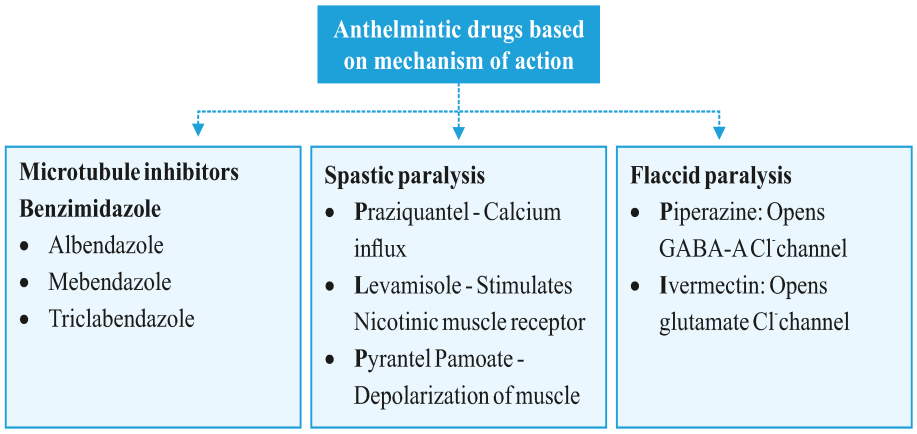
PYQ: FMGE 2019, 2021



Neurocysticercosis

- Occurs when Tinea solium enters the brain
- Giving Albendazole initially will start an inflammatory reaction, leading to death
- First corticosteroids to prevent inflammation and then Albendazole is given to kill the worms following this a course of corticosteroids along with Anti-epileptic drugs (Phenytoin) for 6 months

00:08:40



Benzimidazole (broad-spectrum drug)

00:12:00

MOA

- Microtubule inhibitor → inhibits cell division
- Depletes glycogen stores reducing energy and ATP production leading to worm death by starvation

Pharmacokinetics

- Oral drug → Poor BA (2%)
- Given with juice to increase absorption
- Most common drugs → kill adult + larvae of helminths

Side effects

- Hypersensitivity (m/c)
- Hepatotoxic
- Can cause bone marrow separation (aplastic anemia)

In pregnancy

- Albendazole and Mebendazole are contraindicated in the 1st trimester of pregnancy.
- In 2nd and 3rd trimester they can only be given in severe cases

In children

- Albendazole is contraindicated for < 1-year-old children the most commonly used drug for mass deworming of school children
- Mebendazole is contraindicated for < 2-year-old children

Mass Deworming

- Albendazole
  - >2 years: 400 mg oral tablet
  - 1-2 years: 200 mg oral tablet
- Mebendazole
  - > 2 years: 100 mg oral tablet

Praziquantel 00:17:10

- **MOA:** Calcium influx causing spastic muscle paralysis
- DOC for all cestodes and trematodes
- Contraindicated in ocular cysticercosis as it causes eye inflammation leading to blindness

Niclosamide

- 2nd line drug for cestodes

Metrifonate

- Add-on to Praziquantel
- Used in treatment of Schistosomia hematobium infection

Oxamniquine

- Add-on to Praziquantel
- Used in treatment of Schistosomia mansoni infection

Levamisole

- 2nd line drug for treatment of Ascariasis
- **MOA:** Stimulates Nm receptor causing spastic paralysis
- A low dose of levamisole is an immunostimulant
- Sometimes given in the treatment of steroid-resistant nephrotic syndrome
- **High dose effect:** Immunosuppression → bone marrow suppression (agranulocytosis)

Pyrantel pamoate

- 2nd line drug for Nematode infection

Piperazine

- Used for treatment of Ascariasis and Entrobius

Ivermectin

- **MOA:** Opens glutamate Cl^- channel leading to flaccid muscle paralysis
- Given in the treatment of Scabies, Strongyloides, Onchocerca volvulus
- **Side effects:** Seizures (by opening glutamate Na^+ channel in humans)
- Contraindicated in pregnancy and <5 years children

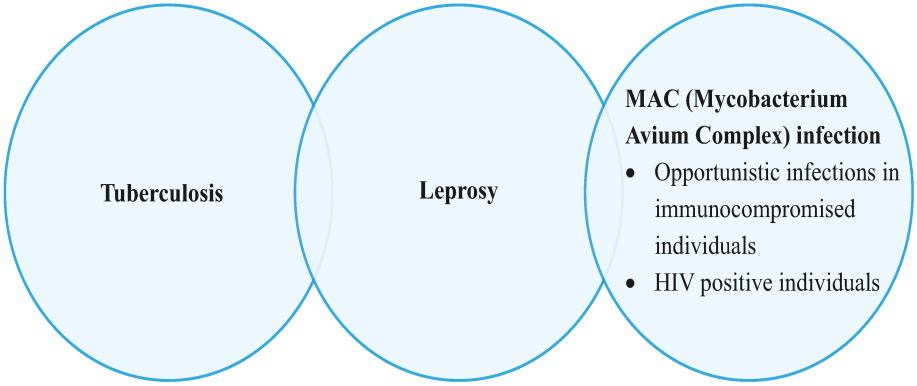
Drugs for scabies 00:24:05

Topical drugs	Oral drugs

• Permethrine (5%) lotion → DOC
  ○ Also used for head lice
  ○ Safe in pregnancy and can be given to children
• Lindane (Benzine hexachloride)
• Benzyl benzoate
• Crotamiton
  ○ The above drugs are not given during pregnancy or to children
	Ivermectin

13 MYCOBACTERIAL INFECTION: TUBERCULOSIS, LEPROSY AND MAC PART-1

Mycobacterial Infections



Tuberculosis

00:00:30

Causative agent	Mycobacterium tuberculosis
Drugs	Anti-tubercular Therapy
Guidelines	NTEP- National Tuberculosis Elimination Program Similar to WHO guidelines

First line drugs

Used in
- In the treatment of new cases of TB
- Drug susceptible TB

Drugs
- H- Isoniazid
- R- Rifampicin
- Z- Pyrazinamide
- E- Ethambutol

ROA
- HRZE is used as a fixed-dose drug and is given orally.

S- Streptomycin
- An injectable given IM
- Used earlier, now not recommended as first-line drug.
- Given as a supplementary drug only if HRZE is toxic or allergic

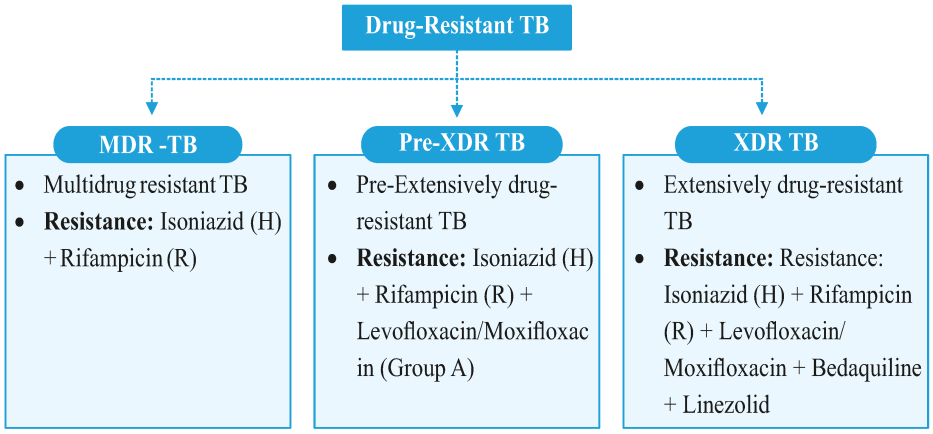
Important Information
- HRZS are bactericidal drugs and Ethambutol is a bacteriostatic drug

Second-line drugs Anti-TB drugs

00:06:20

- Used in the treatment of drug-resistant TB (resistant to first-line drugs)

Groups	DRUGS	Remarks
Group A: BeLL	• Bedaquiline • Linezolid • Levofloxacin/Moxifloxacin	The most effective drugs for Drug resistant TB
Group B: CC	• Cycloserine • Clofazimine	Combined with Group A drugs to complete 5 drug regimen
Group C: DAMPEEP	• Delamanid (New: Pretomanid) • Amikacin • Meropenem, Imipenem • PAS (Para Aminosalicylic acid) • Ethionamide • Ethambutol • Pyrazinamide	Complementary drugs for Group A and B
Other drugs FACKIT	• FQ: Ciprofloxacin, Gatifloxacin • Amox-Clav (Amoxicillin, Calvulanic acid) • Capreomycin • Kanamycin • Isoniazid (High dose) • Thioacetazone	Not used, not effective



Treatment of Drug-Susceptible TB (New case of TB)

PSM 00:16:45

Pulmonary TB

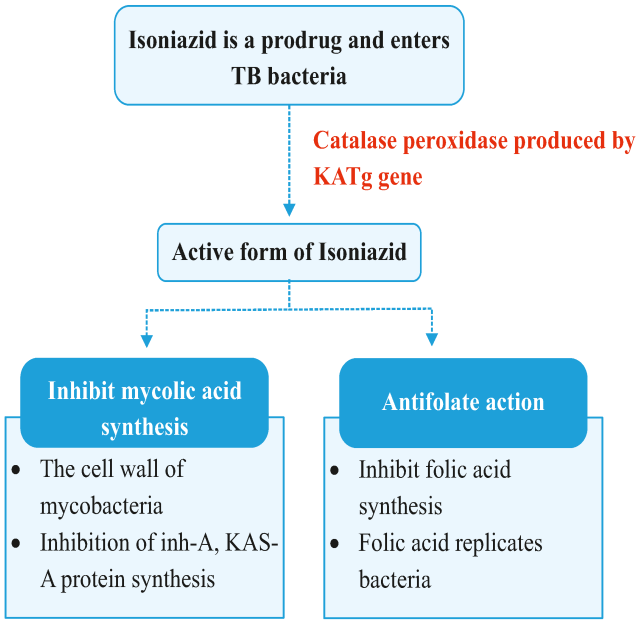
- Involves lungs
- **Intensive phase**
  - HRZE: 2 months
- **Continuous phase**
  - HRE: 4 months
- Total duration: 6 months

Extrapulmonary TB

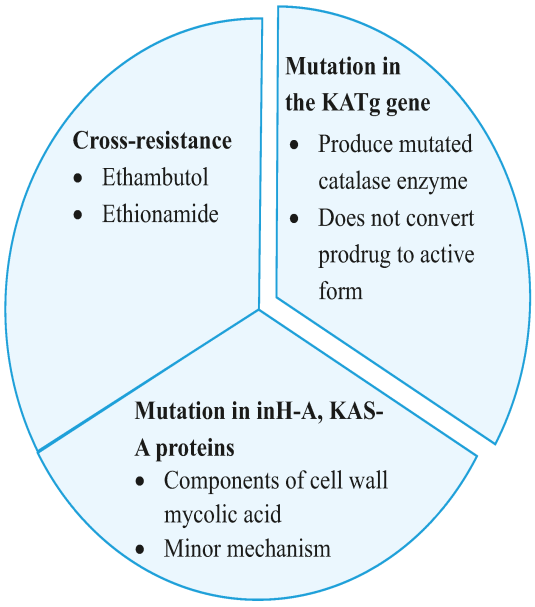
- Other than lungs
- **Intensive phase**
  - HRZE: 2 months
- **Continuous phase**
  - HRE: 7-10 months
- Total duration: 9-12 months

Isoniazid (H)

00:20:05



- **Resistance**:



- **It is administered orally**
- **Metabolization in the body**
  - Isoniazid reduces the activity of CYP enzymes
    → CYP inhibitor
    → Exception: CYP2E1 inducer
    → Increases hepatotoxicity with paracetamol- Paracetamol is converted to NAPQi (hepatotoxicity) by CYP2E1
  - Acetylation by NAT (N-Acetyl Transferase) enzyme in phase 2 reaction

Fast acetylators	Slow acetylators
Good quantity	Poor quantity
Americans	Indians
Low risk of toxicity • Rapidly Metabolized • Removed quickly • Drugs do not accumulate • Drug acetylated	Higher risk of toxicity • Not metabolized • Not Removed quickly • Drug get accumulated • Do not get acetylated
High risk of resistance to TB	Toxicity • Neurotoxicity • Hepatotoxicity

- **Toxicity** of Isoniazid

N	• Neurotoxicity
O	• Optic neuritis: Ethambutol >> Isoniazid
H	• Hepatotoxicity
A	• Anemia (Sideroblastic)
S	• SLE or DLE (SHIP drugs in acetylation)
H	• Hallucinations due to neurotoxicity in the brain
T	• Transient memory loss due to neurotoxicity in the brain
A	• Arthralgia
G	• Gynaecomastia • CYP enzymes produce estrogen

- **Neurotoxicity of Isoniazid**

More common in

- Slow acetylators
- Malnourished
- Children

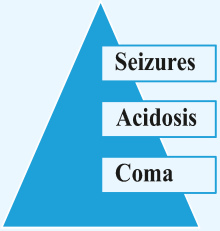
Manifests as peripheral neuropathy

- Numbness
- Tingling
- Paresthesia
- Isoniazid inhibits Pyridoxal phosphokinase (Vit B6) in neurons

Treatment

- Antidote: Vitamin B6 (Pyridoxine)
- Treatment of neurotoxicity- Dose: 100 mg
- In India, vit B6 is given for prevention- Dose: 10 mg in adults
- In children and pregnancy require high doses- Dose: 25-50 mg

Triad of Isoniazid toxicity



- Acute toxicity
- Antidote: Vit B6- 100 mg
- Seizures are resistant to antiepileptics

Rifampicin ®

00:37:15

MOA

- Inhibit DNA-dependent RNA polymerase enzyme produced by rpo-B gene, thereby inhibiting RNA synthesis

Resistance

- Mutation in rpo-B gene
- CBNAAT: Test for detecting mutation rpo-B gene
  - Cartridge-Based Nucleic Acid Amplification Test is a PCR test
  - Used in
    - → Diagnosis of TB
    - → Resistance to Rifampicin

MDR-TB

- Rifampicin + Isoniazid = Synergism
  - Isoniazid inhibits cell wall
  - Rifampicin easily enters inhibiting RNA polymerase
- MDR- TB is resistance to Isoniazid and Rifampicin

- **Uses**
  - Rifampicin is a broad-spectrum drug

Tb	• TB
L	• Leprosy
A	• Anthrax
M	• Meningitis prophylaxis caused by Hemophilus influenzae (Community-acquired in endemic areas)
B	• Brucellosis
D	• Diphtheria- Resistant to Erythromycin (DOC)
A's	• All Staphylococcus (Methicillin-Resistant Staphylococcus aureus)

- **Properties**
  - CYP enzyme inducer
    → Increase metabolism and reduces the activity of drugs
  - P-glycoprotein inducer
    → Increase removal of drug in urine and bile reducing the effect
    → Digoxin: urinary excretion
- **Drug interactions**

Drug	CYP enzymes	Interaction	Management
Estrogen (OCP)	CYP3A4 enzyme metabolism	• Increased degradation of estrogen • Contraceptive failure	• Increase dose • Use other methods of contraception-Copper T, Barrier method
Warfarin	CYP2C9 enzyme metabolism	• Reduce the effect	• Shift to Heparin
HIV drugs		• Reduce the effect	
Isoniazid		• Increased risk of hepatotoxicity	

- **Adverse effects**

Orange color to Red colored urine

- Harmless- Do not stop ATT

Hepatotoxic

Hypersensitivity (Allergy): STOP Rifampicin

- Flu-like symptoms (Most common- Nausea > Rashes)
- Cutaneous syndrome
  - Thrombotic thrombocytopenic purpura (TTP)
  - Intestinal nephritis
- Pulmonary syndrome: Hypoxia, Shock

Rifamycin group 00:50:00

- Inhibits RNA polymerase enzyme
- Drugs are in orange color

Rifampicin	Rifapentine	Rifabutin	Rifaximin

• Used in TB, leprosy
• Strong CYP inducer
• Food decreases absorption (Given in empty stomach)
	• Used in the prophylaxis of TB
	• Weak CYP inducer
	• Increased absorption with food
		• Used in MAC infection
		• Weakest inducer (least drug interaction)
		• No interaction with food
			• Used for gut sterilization as it kills GIT bacteria
			  ○ In hepatic encephalopathy
			  ○ In dysbiosis- IBS
			  ○ Traveller's diarrhea
			• No effect on CYP
			• No interaction with food

- **Hepatic encephalopathy**
  - Gut bacteria produce ammonia and ammonia levels increase in liver diseases.
  - Ammonia not degraded to urea leading to brain damage
- **Pseudo-jaundice**
  - Deposition of Rifabutin the skin gives orange-yellow color Rifabutin
- **Panuveitis**
  - Rifabutin damages the eyes

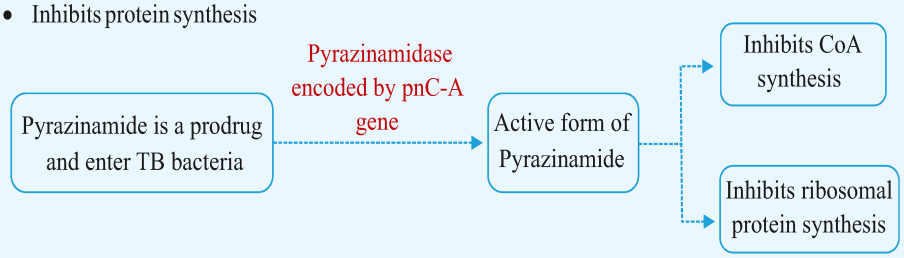
Pyrazinamide (Z) 00:55:10

Old MOA

- Inhibits cell wall and cell membrane synthesis

Main MOA

- Inhibits protein synthesis



Resistance

- Mutation to pnC-A gene: Prevents activation of Pyrazinamide

Uses

- Used only in TB
- Most toxic first-line drug

Side effects

- Most hepatotoxic drug (Z > H > R)
- Maximum risk for hyperuricemia (Z > E)
  - High uric acid level
  - Gouty arthritis- Pain and inflammation in joints

In a patient on Pyrazinamide therapy for TB developing Gout add Allopurinol and do not stop Pyrazinamide.

Ethambutol (E)

01:00:50

MOA

- Inhibits Arabinosyl transferase 3 enzyme responsible for arabinogalactan, a component of the cell wall of TB bacteria
- Reduces arabinogalactan synthesis, thus reducing cell wall synthesis
- Arabinosyl transferase 3 enzyme is encoded by emb-A gene

Resistance

- Mutation in emb-A gene

Side effects

- In eye (painless loss of vision)
  - Red-green color blindness
  - Retrobulbar optic neuritis
  - Reduced visual acuity
- With Ethambutol Vitamin B12 is prescribed as supplementation

Streptomycin (S)

01:04:50

- Aminoglycoside
  - Aminoglycosides used in TB
    - → Streptomycin (as a supplemental drug)
    - → Amikacin
    - → Capreomycin
    - → Kanamycin
    - → Second-line drugs for drug-resistant TB
  - Aminoglycosides are the only injectable drugs in TB
  - Contraindicated in pregnancy as they cause fetal ototoxicity
- Uses
  - Used as a supplemental drug supplement 1st line drugs (HRZE), especially in liver damage

H	R	Z	E	S
Use: Kills intracellular (macrophages) and extracellular (cavities) TB bacteria	Kills both intracellular and extracellular TB bacteria	Kills only intracellular TB bacteria – only acts in acidic pH – inside macrophage pH is acidic	Kills both intracellular and extracellular TB bacteria	Kills extracellular TB bacteria in the cavity – streptomycin can not cross macrophages
To kill rapidly dividing bacteria – Rapid multipliers	To kill Spurturs – suddenly grow in presence of oxygen	To kill slowly dividing bacteria	To prevent the emergence of resistance	To kill rapid multipliers
Dose: 5 mg/Kg	10 mg/kg	25 mg/kg	15 mg/kg	15 mg/kg
Avoided in liver diseases	Avoided in liver diseases	Avoided in liver and renal disease	Avoided in renal disease	Avoided in renal disease

Q. Which of the HRZES drugs has maximum CNS penetration?
Ans. Isoniazid (Cause neurotoxicity)

Q. What is the advantage of isoniazid's rapid killing of bacteria?
Ans.

- 99% of TB bacteria are rapidly dividing and Isoniazid causes a sudden fall in bacterial load (Only 1% of bacteria remain)
- Low bacterial count cannot transfer the infection to another person
- Rapid improvement in TB within 5-10 days
- Reduces the risk of transmission

Q. Which drugs kill the remaining 1% of slowly dividing or dormant bacteria?
Ans. Those drugs have sterilizing action

- Rifampicin- maximum sterilizing action
- Pyrazinamide
- Bedaquiline

- ATT causing liver damage: Known as DILI- Drug-induced liver injury
- Most hepatotoxic: Pyrazinamide > Isoniazid > Rifampicin
- Suspect liver damage: LFT (AST/ALT) > 5 times upper limit of normal
- Management:
  - Stop ATT and Start SLE: Streptomycin, Levofloxacin, and Ethambutol
  - Slowly reintroduce ATT when LFT becomes normal
    → 1st Rifampicin followed by Isoniazid and Pyrazinamide (only if TB causing meningitis)

TB in Renal disease

- Pyrazinamide, Ethambutol, and Streptomycin are avoided
- Safest ATT in renal disease
  - Rifampicin > Isoniazid as they are excreted mainly in bile

TB in pregnancy

- **Same treatment:** HRZE + a high dose of Vitamin B6 (25-50 mg)
- Contraindicated: Aminoglycosides (Streptomycin, Amikacin)
- Ethionamide (2nd line drugs)
  - Contraindicated only in 1st trimester
  - Cause congenital defects

Corticosteroids in TB

- In TB, corticosteroids reduce the signs and symptoms of inflammation
- Corticosteroids
  - Mandatory in Meningeal TB to prevent fibrosis/edema of the brain due to meningitis leading to death
  - Genitourinary TB
  - Spinal TB
  - Pleural and pericardial TB
- Corticosteroids contraindicated in Intestinal TB as they cause intestinal perforation
  - Fibrosis is necessary in intestinal TB and steroids prevent that fibrosis

TB with HIV co-infection

- TB is the most common opportunistic infection in India
  - Opportunistic infections must be treated first
  - Start ATT and start Antiretroviral therapy after 2 weeks
- If ATT and ART are started simultaneously
  - ART increases lymphocyte count leading to the killing of TB
    → Inflammation occurs suddenly that can be dangerous
  - Gap is given to prevent sudden inflammation
- Drug interactions occur between ATT and ART
  - Rifampicin increases metabolism of other drugs as it is a CYP inducer and effect of ART drugs is reduced
  - NRTI (Zidovudine, Tenofovir) and NNRTI (Efavirenz) are safe to give along with Rifampicin
  - Increase dose of the drugs metabolized by CYP
    → Nevirapine (NNRTI)
    → Dolutegravir (integrase inhibitor)
    → Protease inhibitor (Ritonavir, Indinavir, lopinavir)

- Shift Rifampicin to Rifabutin
  - Not a CYP inducer
  - No need of dose increase of ART drugs

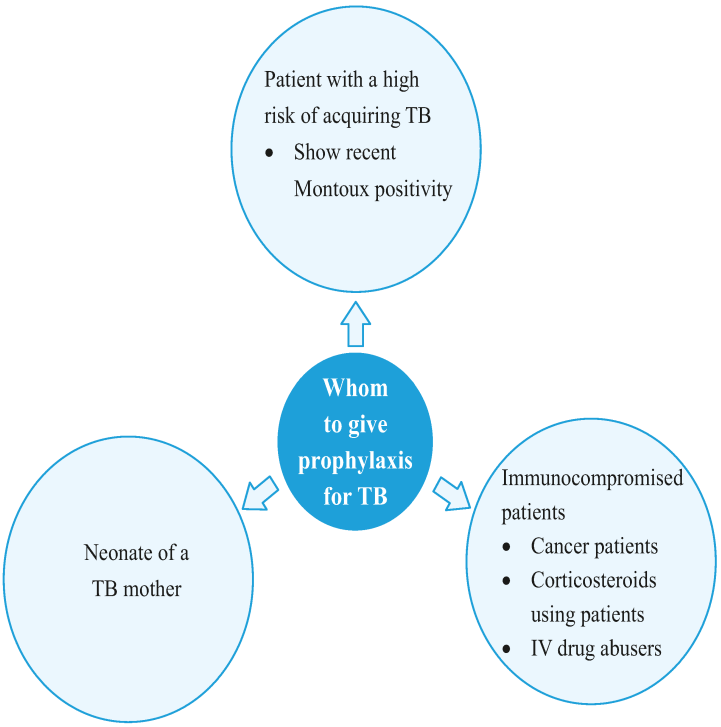
Isoniazid
- Once a day for 6 months

Rifampicin
- Once a day for 4 months

Prophylaxis of TB- Given orally, total 12 doses

Isoniazid + rifampicin
- Once a day for 4 months

Isoniazid + Rifapentine (new combination)
- Once a week for 3 months



14 MYCOBACTERIAL INFECTION: TUBERCULOSIS, LEPROSY AND MAC PART-2

Second Line ATT Group A: BeLL

- Bedaquiline, Levofloxacin or Moxifloxacin, Linezolid
- Highly effective for DR-TB: MDR (Multidrug Resistant) TB

Bedaquiline

00:00:50

MOA

PYQ: FMGE 2023

- Inhibits mycobacterial ATP synthase (ATP proton pump), reducing energy production inside TB bacteria

Resistance

- Mutation in ATP synthase enzyme
- Cross-resistance is seen with Clofazimine

Pharmacokinetics

- Oral drug
- Metabolized by CYP3A4
- Rifampicin is an inducer of CYP3A4 thereby reducing the effects by degrading Bedaquiline

Side effects

- Most common: Nausea
- Most characteristic: QT prolongation

Dose of Bedaquiline

- 0-2 weeks- 400 mg daily
- 3-24 weeks- 200 mg thrice a week
- Given only for first 6 months of treating MDR- TB
- Approved in children in all age groups (Earlier >8 years)
- Avoided in pregnancy/lactation
- Given in HIV positive individual

Fluoroquinolones (Levofloxacin or Moxifloxacin)

00:06:30

- Moxifloxacin is the most effective in treating MDR -TB
- Levofloxacin is safe in liver failure.
- Moxifloxacin is eliminated in bile which may lead to hepatotoxicity
- Other fluoroquinolones used are Gatifloxacin and Ofloxacin under Group D.

Linezolid 00:08:15

MOA

- Inhibits protein synthesis by binding to 23s subunit of 50s ribosomes and inhibits methionine tRNA attachment
  - Methionine is the first amino acid required to initiate protein synthesis

Dose in MDR-TB

- 600 mg oral, OD

Side effects: COMB

- Chorioretinitis
- Optic neuritis
- MAO (Monoamine oxidase) enzyme inhibitor
- Bone marrow suppression (platelet count is monitored)

Group B 00:10:47

Cycloserine

MOA

- Inhibits Alanine resinase, and Alanine ligase enzymes and in turn decreases or reduces cell wall synthesis
- These amino acids produce proteins as part of the cell wall.

Side effects

- CNS: highly neurotoxic
  - Seizures
  - Psychosis- Increased risk of suicide

Terizidone

- Dimer of cycloserine
- Used in treating TB
- Better absorption

Q. For neurotoxicity, pyridoxine (Vitamin B6) is given with which TB drug for treatment

Ans. ICE PYQ: FMGE 2021

- Isoniazid
- Cycloserine
- Ethionamide

Clofazimine 00:13:18

Uses

- Second-line drug in TB and First-line drug in leprosy

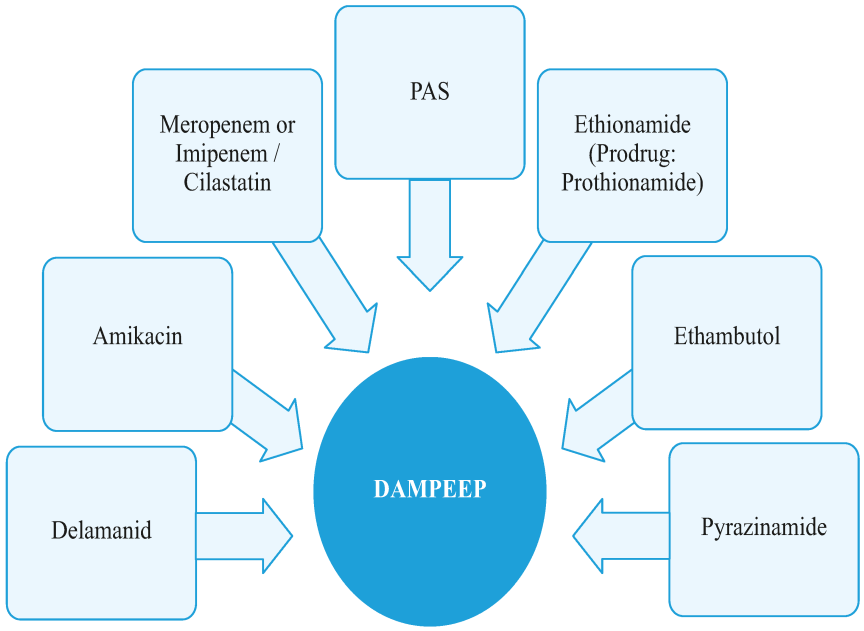
MOA

- Inhibits cell membrane of TB bacteria
- Decreases ATP production
- DNA damage

Side effects

- Brown-red colored Skin, Urine, Sweat, Saliva
- Crystalizes and deposits in GIT causing diarrhea

Group C 00:15:00



Delamanid

MOA

- Similar to Nitroimidazole
- It produces Nitric oxide that inhibits cell wall or mycolic acid synthesis

Uses

- Recently approved for MDR-TB in India

Contraindications

- Latest update contraindicated in children: 3-5 years, Pregnancy and lactation

Side effects

- Similar to Bedaquiline
- QT prolongation

Pretomanid

- Named so as it was made in Pretoria, South Africa
- A new drug similar in action to Delamanid
- Recently introduced in India under the BPal regimen
- Side effects
  - Peripheral neuropathy
  - Acne

Dose

- Delamanid: 100 mg BD, 6 months on OBR (On Background Regimen)
- Pretomanid: 200 mg OD, Bpal regimen

PAS

- Para amino Salicylic acid
- The first drug made for TB
- MOA is similar to sulfonamide- An antifolate drug that inhibits folic acid synthesis in bacteria

Ethionamide

00:19:58

PYQ: INICET 2020

MOA

- Cell wall synthesis inhibition similar to Isoniazid

PYQ: INICET 2022

- Shows Cross-resistance to Isoniazid

Side effects: ETH

- Erectile dysfunction- Impotence
- Thyroid abnormality- Hypothyroid goiter
  - Ethionamide is derived from an Antithyroid drugs group called Thionamide that contains Methimazole and Carbimazole
  - Methimazole and Carbimazole inhibit T3 and T4 synthesis causing Hypothyroidism
  - TSH hormone levels increase leading to increased size of thyroid gland- Goiter
- Hepatotoxic

Other drugs

PYQ: AIIMS 2020

- Thioacetazone

- Only TB drug contraindicated in HIV as it causes severe allergy, rashes
- It is a Bacteriostatic drug

Important Information

Cross-resistance among ATT

1. Isoniazid Ethambutol
2. Isoniazid Ethionamide
3. Ethionamide Thioacetazone
4. Bedaquiline Clofazimine

Treatment of Drug-resistant TB

PSM and Medicine

00:25:10

Mono-Drug resistance

- Isoniazid resistant TB
  - Treatment: RZE + Levofloxacin
  - Given for 6 months daily
- Rifampicin resistant TB
  - Treated like MDR-TB

MDR-TB

- Isoniazid + Rifampicin resistant TB
- Most preferred treatment for MDR-TB
  - BPaL-M regimen
    → Most preferred treatment but not available throughout India
  - Give all oral Bedaquiline containing regimen
    → Common regimen used in India
  - Earlier, longer injectable regimen to TB was used
    → Contains aminoglycosides
    → Not recommended now

Pre-XDR TB

- TB also resistant to Levoflox and Moxiflox
- Bpal regimen given
- If not available
  - Give all oral Bedaquiline containing regimen

00:29:57

BPaL-M

Drugs

- Bedaquiline
- Pretomanid
- Linezolid
- Moxifloxacin is given in MDR-TB and avoided in Pre-XDR TB

Duration

- Continued for 6 months
- If patient still has TB after 6 months, it is extend till 9 months

Used in

- Pulmonary TB
- HIV positive patients

Contraindications

- Pregnancy
- Lactation

9 Month all Oral Bedaquiline Containing Regimen

00:31:40

- Given when the BPaL-M regimen is not available
- The first 4 months of the intensive phase followed by 5 months of the continuation phase
- Drugs:

C	• Clofazimine
E	• Ethionamide
L	• Levofloxacin
E	• Ethambutol • Not given in continuation phase
B	• Bedaquiline • Stopped after 6th month
In	• Isoniazid (high dose) • Not given in continuation phase
Paris	• Pyrazinamide

Longer TB Regimen

00:34:05

PYQ: FMGE 2021

- Contains injectable aminoglycosides
  - Amikacin
  - Kanamycin
- No longer recommended as per NTEP
- It was given for 18-24 months

Leprosy

00:35:05

Causative agent

- Mycobacterium leprae

Other name

- Hansen disease

Guidelines for leprosy treatment in India

- NLEP guidelines
- National Leprosy Eradication Programme

Drugs for leprosy

- MDT- Multidrug therapy

Classification based on

	Paucibacillary leprosy	Multibacillary leprosy
Skin lesions • Have hypopigmented anesthetic macules	1-5	6
Palpable Nerves • Nerve thickening present	0-1	2

Treatment

- Paucibacillary leprosy- RDC for 6 months
- Multibacillary leprosy- RDC for 12 months

First-line drugs for leprosy

00:38:30

RDC	Adult >14 years	Children 10-14 years	Children < 14 years Children < 40 kg
Rifampicin • Given once a month • Taken under supervision	Dose: 600 mg	Dose: 450 mg	Dose: 300 mg
Dapsone • Taken daily • Unsupervised	Dose: 100mg	Dose: 50 mg	Dose: 25 mg
Clofazimine • Both supervised and unsupervised	Dose: 300 mg once a month under supervision Dose: 50 mg daily dose unsupervised at home	Dose: 150 mg once a month and 50 mg on alternative days	Dose: 100 mg once a month under supervision 50 mg twice a week

Second-line drugs for leprosy

00:42:20

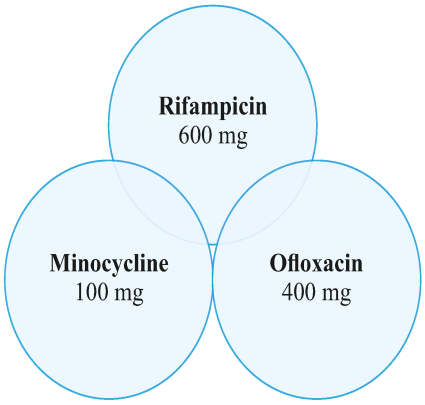
- **Drugs**
  - **C**larithromycin/Azithromycin (Not effective in TB)
  - **O**floxacin
  - **M**inocycline
  - **E**thionamide
- **Bactericidal leprosy drugs**
  - Rifampicin
  - Ofloxacin
  - All other drugs for leprosy are bacteriostatic

WHO - Single lesion Paucibacillary

PSM

00:43:35

- **Single lesion Paucibacillary**
  - If the patient has 1 skin lesion with 0 nerve involvement
  - In India - treatment similar to paucibacillary: RDC for 6 months
  - WHO has given ROM therapy for single-lesion Paucibacillary
- ROM therapy – given as a single dose



Post Exposure to Leprosy Prophylaxis

- Especially for healthcare professionals (Lab technicians, Doctors, Nurses)
- Rifampicin 600 mg single dose

Leprosy vaccine

- MIP vaccine
  - Mycobacterium indicus pranii
- BCG vaccine
  - Protects against leprosy
  - But it is main use is for TB

Dapsone

00:46:30

Class

- Sulfonamide
  - Antifolate drug: Inhibits folic acid synthesis inside TB bacteria

Route of administration

- Oral drug taken unsupervised

Special preparation

- ACE Dapsone- To improve adherence of Dapsone
- Given as IM once in 3 months

Uses- DOC for

- Leprosy
- Protozoal infection
  - Pneumocystis jirovecii
  - Madura foot
  - Toxoplasma
- Dermatitis herpetiformis
  - Due to its immunosuppressive action, it reduces immunity and prevents hyper immune reaction

Pharmacokinetics

- Dapsone is SHIP-DP drug that undergoes acetylation

Side effects

- Drug-induced lupus erythematosus
- Hemolytic Anemia- most common side effect
  - As dapsone causes hemolysis of RBC it is contraindicated in G6PD deficiency patients
- Antidote for hemolytic anemia: Methylene Blue

Dermatitis herpetiformis- skin lesions in the extensor aspect of the forearm

- Seen in gluten-sensitive individuals
- DOC: Dapsone- Orally

Leprae Reaction

00:51:25

- Leprae reaction- Hypersensitivity to MDT (leprosy drugs)

Type 1 Leprae reaction	Type 2 Leprae reaction
Type 4 hypersensitivity reaction • Cell-mediated immunity suddenly starts working	**Type 3 hypersensitivity reaction** • Immune complexes are produced and deposited in the organ
• Also known as the reversal reaction	• Also known as ENL (Erythema Nodosum Leprosum)
Treatment: • Do not stop MDT • DOC: Corticosteroid- Prednisolone • In mild hypersensitivity, other anti-inflammatory agents are given in place of corticosteroids like Chloroquine	**Treatment:** • Do not stop MDT • DOC: Corticosteroid- Prednisolone • In mild hypersensitivity, other anti-inflammatory agents are given in place of corticosteroids like Chloroquine • In corticosteroid-resistant cases, Thalidomide used ○ Inhibits TNF α and reduces inflammation

Mycobacterium Avium Complex (MAC)

00:55:50

- A rare opportunistic infection in HIV-positive individuals
- Occurs when CD4 count falls <50/mm^3 leading to Pneumonia

Treatment	Prophylaxis
• MAC infection	• CD 4 count<50/mm^3 • No MAC infection • The risk of acquiring infection is high
Drugs: CARES FQ • Clarithromycin (more effective) or Azithromycin • Add o Rifabutin o Ethambutol o Streptomycin o Fluoroquinolones (Ofloxacin, Ciprofloxacin)	**Drugs** • Azithromycin once a week **OR** • Rifabutin daily

15 ANTI FUNGALS

Fungal infections

00:00:08

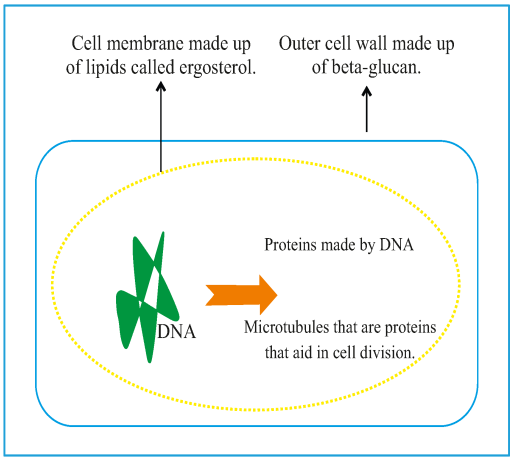
Superficial mycosis	Deep / Invasive mycosis

• Fungus remains on the skin
• Fungi causing superficial mycosis are:
  ○ Candida
  ○ Tinea (also known as Dermatophytosis, Ringworm)
  ○ Tinea versicolor
  ○ Onychomycosis (toe-nail infection)
	• The fungus invades deep into the skin
	• Commonly occurs in immunocompromised patients in the case of
	  ○ HIV
	  ○ Cancer
	  ○ Patient using corticosteroids
	  ○ Undergone bone marrow transplantation

Treatment depends upon the type of fungus invaded

- Yeast like fungi (budding)
- Moulds (spores)
- Dimorphic

Structure of fungi



Cell wall inhibitors

00:04:31

Also knows as

- Echinocandins

MOA

- Inhibit 1,3 beta glucan synthase

Drugs

- Caspofungin, Rezafungin, Anidulafungin, Micafungin

Uses

- These drugs are given I.V. for invasive candidiasis
- Caspofungin is also given to treat aspergillosis

Advantage

- Renal – safe drugs unlike amphotericin B

Side effect

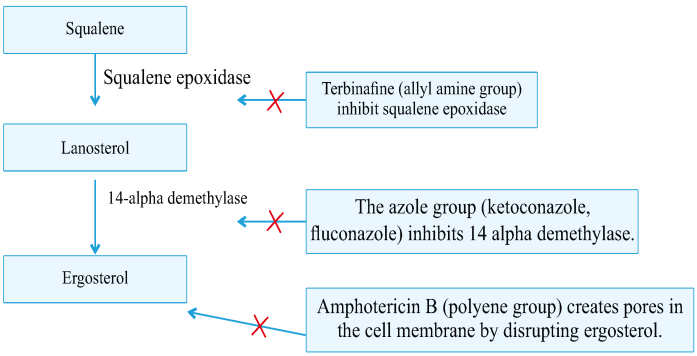
- Hepatotoxic

New oral drug

- "Ibrexafungerp" - used to treat superficial mycosis called vulvovaginal candidiasis

Cell membrane inhibitors

00:08:13



Polyenes

00:11:06

- Create pores in ergosterol membrane
- Highly amphoteric
- Drugs derived from Streptomyces bacteria
  - Amphotericin B
  - Natamycin
  - Nystatin

Natamycin

- Highly nephrotoxic
- Given topically as eye drops
- DOC: For Fungal keratitis

PYQ: FMGE 2022

Nystatin

- Highly nephrotoxic
- Given topically as oral paint 5% in an oral candida infection (in asthmatic individuals caused by corticosteroids)

Amphotericin B

- Derived from Streptomyces nodosus
- Given I.V
- Most effective drug
- Fungicidal drug
- Use- Broad spectrum drug
- **DOC**
  - Serious invasive fungal infection
    - → Cryptococcal meningitis, Mucormycosis, Coccidial meningitis.
    - → IV induction
    - → If improved oral azoles as maintenance

PYQ: FMGE 2021

- Kala-azar: protozoal infection
  - → Leishmania donovani
- Should not be given at home
- In hospitalized patients, a drip of amphotericin B + 5% dextrose is given under supervision.
  - It is insoluble in normal saline and Ringer's lactate.

Allergic reaction (infusion-related reactions)	**Anaemia**
• Including fever, chills, and hypotension • Pretreatment with NSAIDS (paracetamol, ibuprofen), antihistamine, meperidine	• Treatment: recombinant erythropoietin
Side effects	
Azotemia	**Arachnoiditis**
• AKA: Nephrotoxicity • Accumulates and damages nephron's tubular cells leading to RTA (Renal tubular acidosis) • RTA leads to the loss of Mg^{2+}, and K^{+} ions in urine. • Therefore, monitor blood K^{+} and Mg^{2+} levels • Pretreatment: Lots of fluids (normal saline, ringers lactate).	• When Amphotericin B is given intrathecal in meningitis conditions, it damages the meninges causing arachnoiditis.

- **Preparations**

c-AMB (Oldest)	Conventional amphotericin B	Most nephrotoxic
AMB-CD	Amphotericin B colloid dispersion	Infusion reactions (allergy)
AMB-LC	Amphotericin B lipid complex	Less adverse effect
L-AMB	Liposomal Amphotericin B	Safest drug, longest action, costliest drug

Azoles

00:25:17

- **MOA**
  - Inhibit 14 alpha demethylase enzyme (also known as fungal CYP)
  - This enzyme converts lanosterol into ergosterol cell membrane
  - Hence decreases cell membrane synthesis
- **Broad spectrum drugs**
  - Less effective
    - → Compared to Amphotericin B
    - → Fungistatic drugs
- **Pharmacokinetics**
  - All azoles metabolized by the CYP2C19 enzyme
  - Azoles are CYP inhibitors
    - → Maximum CYP inhibiting action - ketoconazole
  - Excreted in bile except fluconazole which is excreted in urine
    - → Renal safe
  - Side effects: Hepatotoxic
  - Fluconazole is contraindicated in renal diseases

IMIDAZOLE		TRIAZOLE PYQ: NEET PG 2019, 2020, 2023	
Topical only	**Topical + systemic (oral and IV)**	**Topical + systemic**	**Systemic only**
• Clotrimazole (Available as a vaginal pessary) • Oxiconazole • Miconazole • Efinaconazole • Luliconazole • Tebuconazole • Sertaconazole • Tioconazole	Ketoconazole	Fluconazole	• Voriconazole • Itraconazole • Posaconazole • Isavuconazole

- Topical imidazoles are DOC in vulvo-vaginal candidiasis
  - Other infections treated are
    - → Tinea
    - → Tinea versicolor
    - → Onychomycosis
- **Sertaconazole has antipruritic effect**

Ketoconazole 00:33:23

- Broad spectrum
- Rarely used nowadays
  - Most toxic Azole
- Still used topically
  - DOC: Dandruff- Seborrheic dermatitis caused by Malassezia furfur
- Properties
  - Maximum CYP inhibiting action
    - → Increase toxicity of other drugs
    - → Most hepatotoxic
  - Steroid hormones are synthesized by CYP enzymes
    - → Ketoconazole inhibits steroid hormone synthesis
    - → Adrenal insufficiency
      - Reduced mineralocorticoid and glucocorticoids
      - Shock occurs due to renal insufficiency
    - → Testosterone
      - Gynecomastia and impotence
    - → Estrogen
      - Menstrual irregularities

Fluconazole 00:36:23

DOC: Yeast like fungi

- Candidiasis
  - Esophageal candidiasis
- Coccidiomycosis and cryptococcal infection
  - DOC: Amphotericin B for induction
  - Fluconazole for maintenance
- Cryptococcal infection
  - DOC: Amphotericin B for induction
  - Fluconazole for maintenance

Side effects

- Avoid in renal failure as it is excreted in urine
- Alopecia

Itraconazole

DOC: Dimorphic fungi

- Divides by budding or spore formation like
  - Blastomycosis
  - Histoplasmosis
  - Sporotrichosis
  - Penicilliosis
- For these DOC: Amphotericin B for induction
  - Itraconazole for maintenance

Side effects

- Skin cancer – squamous cell carcinoma
- Hypertension leading to CHF

DOC: Eumycetoma

- Because Amphotericin B is not effective

Voriconazole 00:39:57

DOC: Moulds/spore forming fungi

- Like aspergillosis
  - First DOC: Voriconazole
  - Better than Amphotericin B
- Cercosporidium
- Trichosporon
  - First Amphotericin B is given
  - Voriconazole for maintenance

Side effects

- Visual hallucinations
- QT prolongation
- Voriconazole and posaconazole contain fluorine and cause fluorosis

Q. Voriconazole is not effective against which mould?

Ans. Mucormycosis (black fungus)

- DOC: IV Amphotericin B
- Alternate drugs:
  - Posaconazole
  - Isavuconazole

Q. What is the treatment for invasive fungal infection in pregnancy?

Ans. Amphotericin B

- Azoles are contraindicated in pregnancy as they are teratogenic.

Terbinafine

00:43:56

MOA

- Inhibits squalene epoxidase
  - Hence inhibits conversion of squalene to lanosterol

Other drugs like Terbinafine

- Butenafine
- Naftifine

ROA

- Oral/topical drug

Uses

- Given for toe-nail infection
  - DOC: in onychomycosis
  - In Tinea – less effective than azoles

Side effects

- Hepatotoxic

DNA: Flucytosine

00:45:39

MOA

- Inside fungal cell – converted to 5 fluorouracil
- Inhibits thymidylate synthase enzyme
- Fungus dies due thymidine deficiency cell death

DOC

- Cryptococcal meningitis
- Amphotericin B (DOC) + Flucytosine

Tavaborole

00:47:40

- Inhibits protein synthesis
- New drug for onychomycosis

Griseofulvin

00:48:06

MOA

- Microtubule inhibitor
- Inhibits cell division
- Fungistatic drug
- CYP inducer

ROA

- Topically
- Orally it goes to skin and binds to keratin protein

Uses

- DOC: Superficial fungal infections
  - Tinea Capitis
    - → Occurs in scalp area
    - → Most effective
  - Tinea cruris
  - Tinea ungris
  - Tinea corporis
    - → Griseofulvin is less effective
    - → Resistance common
  - Tinea versicolor – not effective

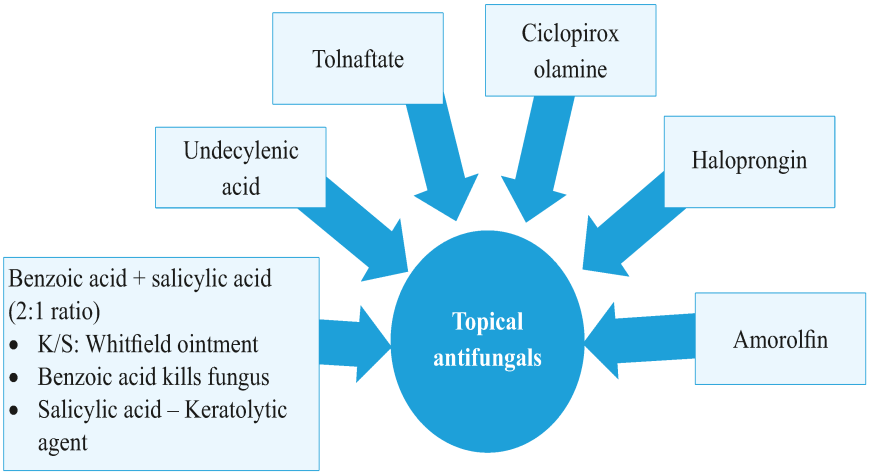
Side effects

- Disulfiram like reaction (avoided in alcoholics)
- Headache

Antifungal prophylaxis in immunocompromised

00:51:28

- Immunocompromised patients
  - Cancer patients
  - Patients taking corticosteroids
  - Advanced stages of HIV and AIDS
- 3 drugs approved for fungal prophylaxis
  - Fluconazole
  - Posaconazole
  - Micafungin

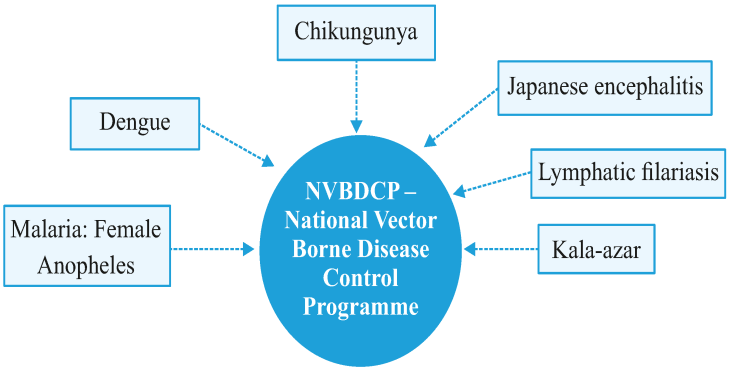


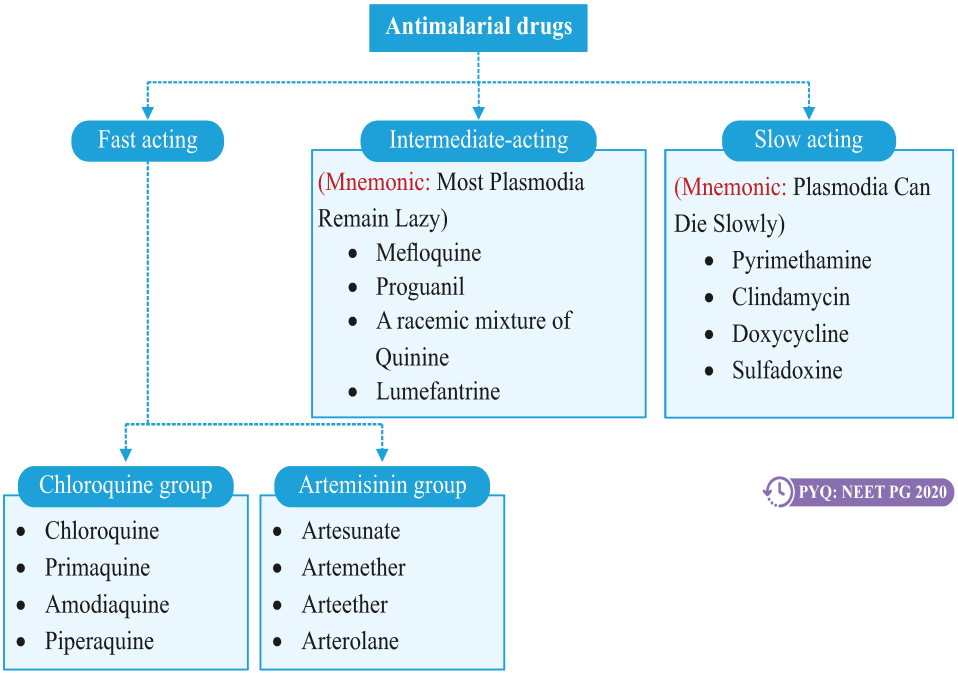
Q. Which antifungal drug is available as nail polish/nail lacquer for Onychomycosis?
Ans. Ciclopirox olamine and amorolfine

16 ANTI PROTOZOANS

Malaria

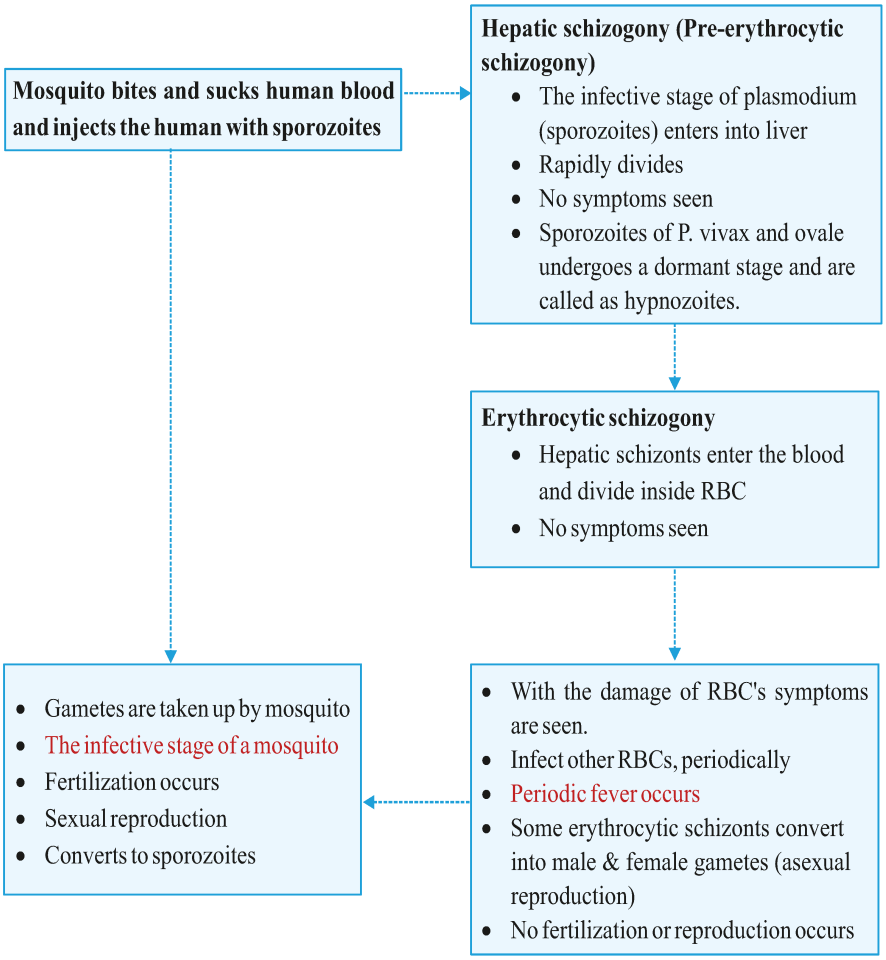
- Causative agent: Plasmodium (a protozoan)
- It has 5 species in human
  - Plasmodium falciparum
    → > 50% cases in India
  - Plasmodium vivax
  - Plasmodium ovale
  - Plasmodium malariae
  - Plasmodium knowlesi





PYQ: NEET PG 2020

- **Drugs available in other countries**
  - Pyronaridine (Mainly China)
  - Atovaquone (America)

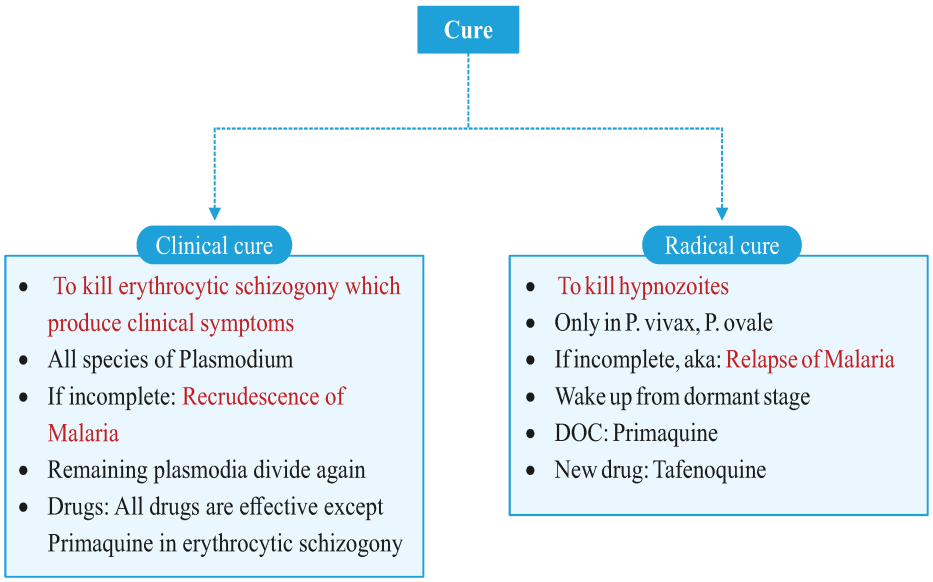


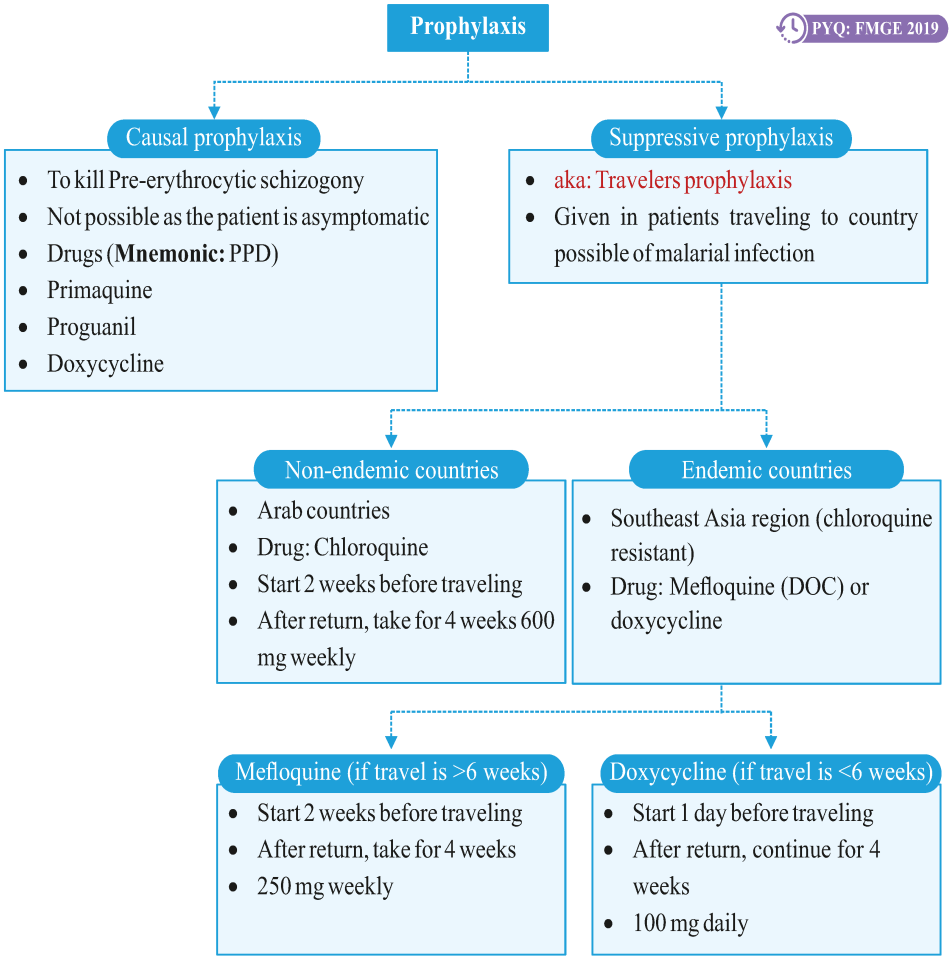
Treatment of Malaria

00:11:20

PYQ: AIIMS 2019

- Cure
- Prophylaxis





Drugs acting against various stages

Hepatic schizogony: Causal prophylaxis	• Primaquine • Proguanil • Doxycycline
To kill hypnozoites: Radical cure	• Primaquine Tafenoquine
To kill Erythrocytic schizogony:	• Clinical cure - All drugs can be given except primaquine
Gametocidal drugs	• DOC: Primaquine ○ Effective against all species ○ Used to prevent transmission of malaria in endemic area
Sporozoites	• No drugs • Vaccine prevents infection • Mosquirix vaccine ○ RTS,S/AS01 ○ Live sporozoites are covered with HBV-Ag ○ Stimulate T cells and induce immune response against sporozoites ○ Given intramuscularly and only in children

P. vivax/Ovale

- Chloroquine + Primaquine
- Chloroquine given for 3 days for Clinical cure.
- Primaquine given for 13 days for Radical cure and as a gametocidal agent.

P. falciparum

- Most common infection in India
- But it is chloroquine resistant
- ACT + Primaquine
- ACT: Artemisinin-based combination therapy (clinical cure)
  - All Indian states
    - → Artesunate + sulfadoxine /pyrimethamine
    - → Fast acting and slow acting combination
  - Except Northeastern states
    - → Artemether + Lumefantrine
- Primaquine
  - Given as gametocidal as there is no hypnozoite stage in P. falciparum

Mixed infection

- P. vivax/ovale/falciparum
- ACT + Primaquine for 14 days

Other approved regimens for Chloroquine-resistant malaria

- Artesunate + Mefloquine
- Artesunate + Amodiaquine
- Artesunate + Pyronaridine (used in China)
- Arterolane + Piperaquine
- QDC regimen: Quinidine + Doxycline + Clindamycin
  - Given in Artemisinin allergic individuals

Q. In Chloroquine-resistant malaria, what are the 2 main drugs?
Ans. Artemisinin group + Quinine

- Plasmodium falciparum

Q. Which is the fastest and most effective drug?
Ans. Artesunate (Artemisinin group)

- Also shortest-acting drug
- Increased risk of recrudescence, especially in P.falciparum

Important Information

- Never give short-acting drugs for prophylaxis or prevention
  - Frequent doses can be avoided
  - The risk of resistance is reduced

Antimalarials in G6PD deficiency

00:36:05

- Antimalarials can cause damage and hemolysis of the RBC in G6PD deficiency
- Most unsafe drug: (**Mnemonic:** PPQ)
  - Primaquine
  - Proguanil
  - Quinine
- Safer: Chloroquine
- Safest: Mefloquine

Complicated malaria (Acute severe malaria)

- P. falciparum causes complicated malaria
  - loss of consciousness
  - Life-threatening condition
  - Injectable drugs are given in life-threatening conditions and in emergencies

Treatment

- DOC: IV Artesunate

PYQ: FMGE 2021

  - Only Artemisinin can be given intravenously
  - Other Artemisinins are given intramuscularly
- 2nd: IM Artemether/Arteether
- 3rd: IV Quinine in 5%Dextrose solution
  - Quinine causes hypoglycemia

Malaria in pregnancy

00:41:18

Safest in all trimesters • Chloroquine • Quinine • Clindamycin	**Contraindicated in 1st trimester** • Artemisinin (ACT), but can be given in 2nd and 3rd trimesters

Contraindicated in all trimesters
• Primaquine
• Doxycycline
	P. vivax/ovale: Chloroquine only
	• Primaquine is contraindicated
	  ○ Radical cure is not given which can lead to relapse
	  ○ Relapse is treated after pregnancy

P. falciparum • Chloroquine resistant • 1st trimester: Quinine + Clindamycin • 2nd or 3rd trimester: ACT	**Complicated malaria** • Life-threatening • IV Artesunate given in all trimesters even in 1st trimester as the life of the mother is more important

Transfusion-associated malaria

00:45:02

- In the blood, only erythrocytic schizogony is present, therefore, only clinical cure is given.
- No role of primaquine as it is not effective in clinical cure since hypnozoites are absent
- Drugs
  - Chloroquine
  - ACT

1. Chloroquine

00:46:25

MOA:

- Plasmodia eats hemozoin. Inside the food vacuole hemoglobin is converted into hemozoin.
  - Chloroquine inhibits the conversion of hemoglobin to hemozoin
  - Hemoglobin in increased amounts becomes toxic to plasmodia

Resistance

- Plasmodium develops a transporter to efflux chloroquine outside the food vacuole
- P_f CRT (P_f Chloroquine Resistance Transporter)

Uses

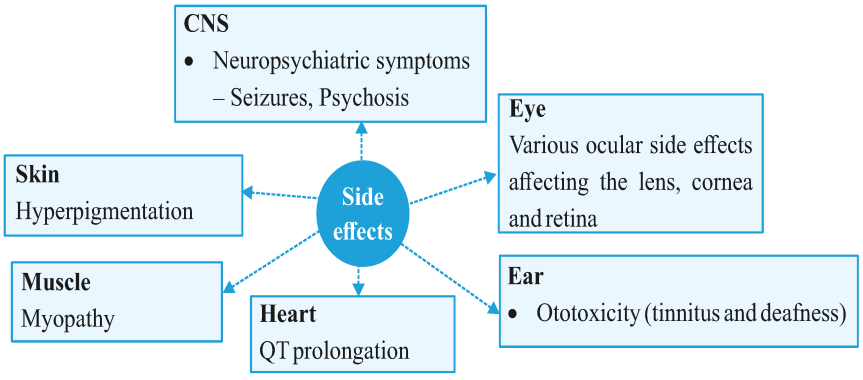
- Protozoan infections
  - Malaria
- Immunosuppressive action by decreasing immunity of the body
  - Inhibits IL-1, 6, TNF alpha production
  - Used in the treatment of autoimmune disease and hypersensitivity

Properties

- Oral and IV forms
- The volume of distribution: 15000 liters of plasma
  - VD is proportional to the amount of drug entering the organ
  - Deposits in various organs, therefore hemodialysis has no role in chloroquine toxicity.

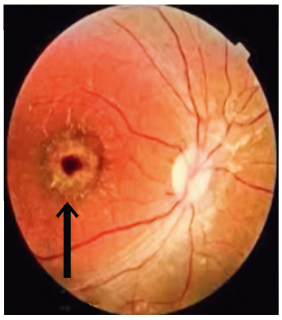
Uses of Chloroquine

M	Malaria (Protozoa)
A	Amebiasis (Amebic liver abscess)
L	Leprae reaction
A	Atopic dermatitis
R	Rheumatoid arthritis
I	Infectious mononucleosis
A	Autoimmune hemolytic anemia
G	Giardiasis (Protozoa)
D	DLE or SLE
P	• Photosensitivity on skin (Polymorphous light eruption)



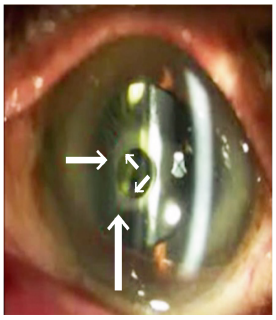
Important Information

- Mefloquine has a maximum risk of Neuropsychiatric symptoms and is contraindicated in cerebral malaria
- Quinine causes maximum ototoxicity, also known as Cinchonism, obtained from cinchona.
- Lumefantrine, Quinine, and Primaquine have a maximum risk of causing QT prolongation

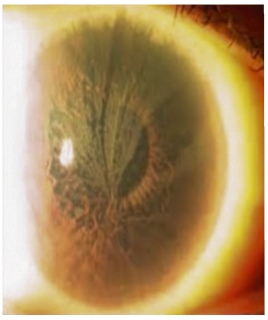


Bull's eye maculopathy

- In the retina, Chloroquine deposits as concentric rings that can cause permanent blindness



Anterior subcapsular cataracts



Vortex keratopathy

Important Information

Amiodarone also causes Anterior subcapsular cataracts and Vortex keratopathy

2. Artemisinin group

00:59:48

Source

- Obtained from Chinese herb called Artesuna annua, by Tu You You (Nobel prize)

Drugs

- Artesunate
- Arterolane
- Artemether
- Arteether
- Di hydro Artesunate

ROA

- All are given orally except Artesunate which can be used IV (used in complicated malaria)
- Artesunate, Artemether, Arthether: IM
- Artesunate: rectally in children, and shock

Pharmacokinetics

- Metabolized by CYP2A6

Side effects

- Common: Nausea and vomiting
- Severe: Allery (Hypersensitivity)
  - Substitute with Quinine

3. Quinine 01:03:20

Pharmacokinetics

- Racemic mixture of L & D form of Quinine
- D form quinine is also known as Quinidine
  - Also used as Class IA antiarrhythmic drug
  - Blocks sodium and potassium channels in the heart
- Metabolized by CYP2D6

Source

- The bark of the cinchona plant

Side effects

- Most commonly diarrhea
- Hypoglycemia
  - Causes insulin release by blocking potassium channel on the pancreas
  - Always given with dextrose
- QT prolongation
  - Blocks potassium channel on heart
- Hypotension
  - Blocks alpha receptor
- Ototoxicity
  - aka: Cinchonism

4. Primaquine

- Effective in all stages of malaria except erythrocytic schizogony
- It is not effective in clinical cure

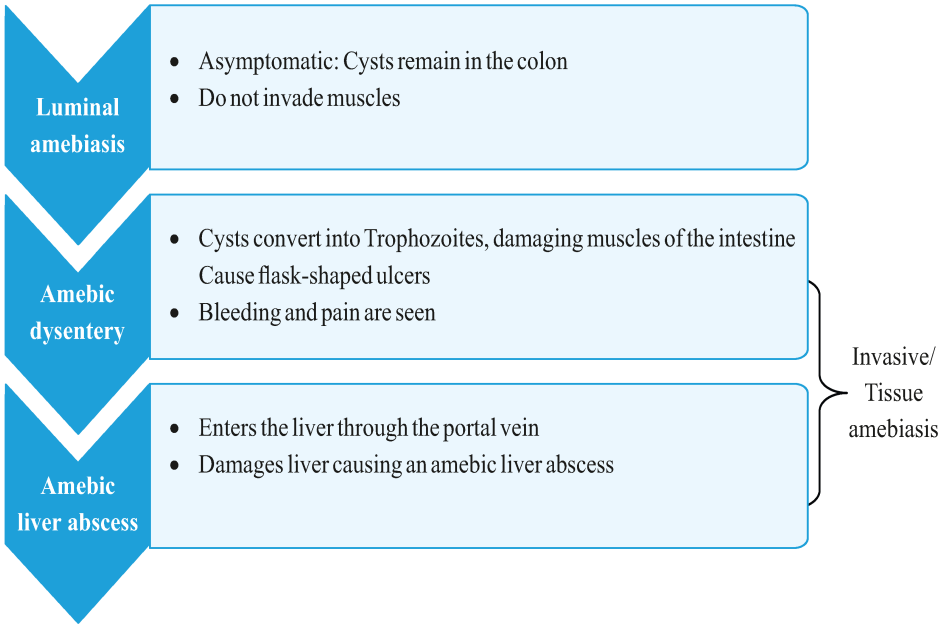
5. Miscellaneous drugs

- Pyrimethamine, Proguanil
  - Antifolate drugs- Inhibits DHFR (Dihydrofolate reductase) enzyme
  - The function of DHFR is the conversion of folic acid into tetrahydrofolate (active form)
  - Always combine folinic acid (tetrahydrofolate) to prevent Megaloblastic anemia
- Doxycycline is contraindicated in pregnancy and children <8 years
- Clindamycin is safe in pregnancy and children
- Lumefantrine is given in Northeastern states of India
  - Treatment of Chloroquine-resistant malaria and Multidrug-resistant malaria (Artemisinin, Quinine)
  - It causes QT prolongation
  - Halofantrine is used outside of India

Amebiasis 01:09:51

- Causative agent Entamoeba histolytica

- Spread
  - Fecal-oral route
  - Unhygienic food and water
  - Cysts of Entamoeba histolytica enters GIT and are converted to trophozoites that damages GIT



Luminal amebicidal drugs	Tissue amebicidal drugs
Kills ameba cysts in the lumen • DOC: Paromomycin • Diloxanide furoate • Quiniodochlor • Iodoquinol	• DOC: Metronidazole or its congeners ○ Used in Amebic dysentery and Amebic liver abscess ○ Chloroquine is an add-on drug for liver abscess • Emetine

Luminal amebicidal drugs

Paromomycin

- Given orally
- Aminoglycoside
- Not absorbed in GIT but kills the Entameba in GIT

Diloxanide furoate

- Furoate is active moiety
  - Kills entameba
- Side effects: Flatulence

Quiniodochlor

- Also known as Clioquinol
- Rarely used due to dangerous side effects
  - SMON (Subacute myelo-optico-neuropathy)

Iodoquinol

- Contains iodine
- Side effects
  - Thyroid abnormalities
  - Allergy (angioedema)

Tissue amebicidal drugs

Metronidazole and congeners (Tinidazole, Ornidazole)

- DOC for
  - Amebic dysentery
    → 400 mg, 3 times a day for a week
    → Add luminal amebicidal drugs
  - Amebic liver abscess
    → 800 mg, 3 times a day, for 10 days
    → Add luminal amebicidal drugs + Chloroquine
    → Chloroquine kills liver-stage

Emetine

- Inhibit protein synthesis in Entamoeba
- Side effects:
  - Vomiting (most common)
  - Cardiotoxic

Trypanosoma

01:20:10

Diseases of Trypanosoma

Sleeping sickness
- Also known as the African type of Trypanosomiasis

Chagas disease
- Also known as the South American type of Trypanosomiasis

African type (Sleeping sickness)

- Transmitted by Tse Tse fly bite

West African type	East African type
Trypanosoma brucei gambiense	Trypanosoma brucei rhodesiense
Enters blood (early stage) → CNS (late stage) causes	Enters blood (early stage) → CNS (late stage) causes
DOC • Early stage: Pentamidine • Late stage: Eflornithine + Nifurtimox **New drug** • Fexinidazole ○ Effective in early, late stages	**DOC** • Early stage: Suramin • Late stage: Pentamidine

Pentamidine

- IV drug for trypanosoma
- Also available as aerosols
- Effective in treatment of Pneumocystis jirovecii infection
- Side effects:
  - Pancreatitis: Hypo/Hyperglycemia
  - Hypotension

Eflornithine

- Treatment of Trypanosoma
- Also used for topical hair removal cream
  - De-epilator in hirsutism
- MOA: inhibit ornithine decarboxylase

Melarsoprol

- Arsenic containing drug toxic to Trypanosoma

South American type (Chagas disease)

- Species: Trypanosoma cruzi
- Charles Darwin died of Chagas disease
- Drugs
  - DOC: Benznidazole
  - Nifurtimox- Also used for sleeping sickness

Pneumocystis jirovecii

01:28:07

- Opportunistic infection in HIV-positive individuals infecting the lungs and producing cavities
  - If CD4 count <200/mm^3 the prophylaxis is started

Drugs

- DOC for treatment and prevention: Cotrimoxazole
  - TMP (Trimethoprim)/SMX(Sulfamethoxazole)
    → 80/200 mg daily or 160/200 mg thrice a week
  - Side effects of cotrimoxazole
    → Sulfa allergy
- Pentamidine aerosols
- Clindamycin + Primaquine (anti-malarial drug)
- Atovaquone (anti malarial drug) + Dapsone (leprosy drug)
- New drug: Trimetrexate
  - Similar to Methotrexate
  - Inhibit DHFR enzyme

Leishmania

01:31:45

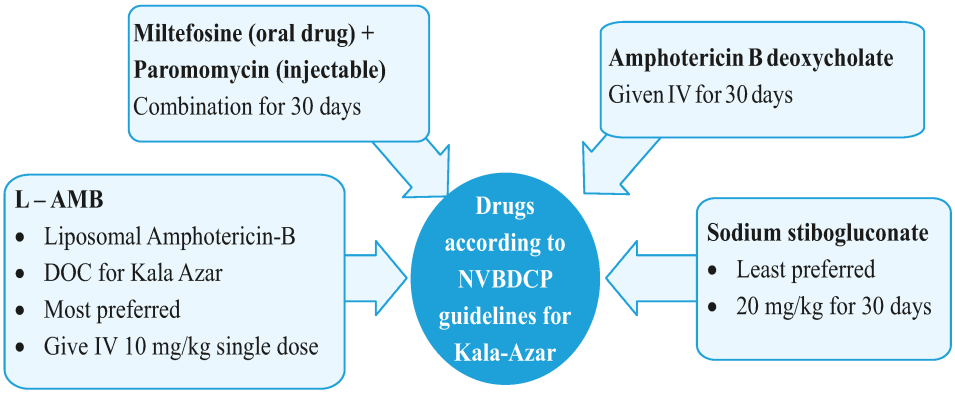
Visceral leishmaniasis	Cutaneous leishmaniasis/ Mucocutaneous leishmaniasis
Spreads inside the body goes into organs	Remains on skin or mucous membrane
Also known as Kala-azar • Highly prevalent in North India	Also known as Oriental sore • Seen in tropical countries, Brazil

Species: Leishmania donovani	Leishmania tropica / brazilensis
Treated under NVBDCP guidelines • Vector: Sandfly mosquito	DOC: Sodium stibogluconate • Resistant against Kala-azar Other drugs • Amphotericin-B • Pentamidine • Paromomycin

Kala-azar (Visceral leishmaniasis)

01:34:25

- Endemic in North India
- Diagnosis: rk39-Rapid diagnostic test
- **Mnemonic: LAMPAS**



Q. DOC for pregnancy and children

Ans. L-AMB

- Liposomal Amphotericin-B

Important Information

Allopurinol is used for the treatment of gout but it was first prepared for Kala-azar

Post Kala-azar dermal leishmaniasis (PKDL)	
	• Not dangerous • DOC: oral Miltefosine ○ CI: Pregnancy, children • In pregnancy/children: L AMB

- Sodium stibogluconate
  - Initially made for kala-azar
  - aka: Pentavalent antimonial
    - → Contains Antimony (Sb) Toxic to leishmania
  - Side effects
    - → QT prolongation
    - → Pancreatitis
    - → Nephrotoxic
  - Resistance in Kala-azar

Trichomonas vaginalis

01:42:06

- Female with abnormal yellow-green vaginal discharge.
- Unpleasant fishy smell.
- Strawberry cervix with punctate hemorrhage
- Treatment
  - Metronidazole 2 g for 5-7 days
  - Tinidazole
  - Treat partner also single dose

Giardiasis

01:43:24

- Causes diarrhea in HIV-positive individuals
- DOC: Metronidazole/Tinidazole
- In pregnancy, DOC: Paromomycin
- Nitazoxanide is used in Immunocompetent patients

Toxoplasma gondii

01:44:38

- Spread through cats
- DOC: Sulfadiazine + Pyrimethamine
  - Antifolate drugs
  - Add folinic acid
- In sulfa-allergic patients, replace Sulfadiazine with clindamycin
- In pregnancy, it crosses the placenta and causes congenital defects.
  - Amniocentesis
    → IgM/IgG antibodies in amniotic fluid against toxoplasma gondii
    - Positive: non treatable
    - Negative: can prevent placental transmission with Spiramycin

Some other protozoans

01:47:35

Babesiosis
- Malaria like illness
- Mild: Atovaquone + Azithromycin
- Severe: Quinine + Clindamycin

Balantidium coli
- Amebiasis like infection
- DOC: Tetracycline

Cyclospora & Isospora
- Diarrhea in HIV-positive individuals
- DOC: Cotrimoxazole

Naegleria
- Amebic meningoencephalitis
- DOC: Amphotericin – B

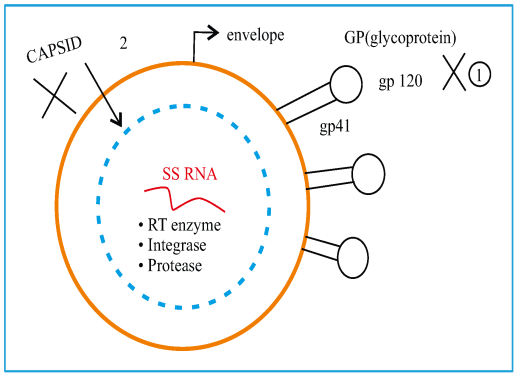
Microsporidia
- Diarrhea in HIV – positive individuals
- DOC: Albendazole
- Topical ulcer: Keratitis
  - DOC: Topical Fumagillin
- Severe sepsis, Inflammation, and allergy
  - DOC: Thalidomide

17 ANTI VIRAL DRUGS

HIV

00:00:47

- Human immunodeficiency virus
- It is of two types
  - HIV 1: More common
  - HIV 2
- Treatment guideline: National AIDS Control Program (NACP)
  - Similar to WHO guidelines



HIV has an envelope.
↓
Spikes of proteins are attached to the envelope - Glycoprotein.
↓
Inside the envelope
The virus has a blue color capsid.
↓
It has single-stranded RNA and three enzymes.

- Two glycoproteins include
  - gp 120
  - gp 41
- Three enzymes: **Mnemonic** RIP
  - **R**everse transcriptase
  - **I**ntegrase
  - **P**rotease

Glycoproteins
↓
Binds to a human cell on the CD4+ receptor with the help of co-receptors

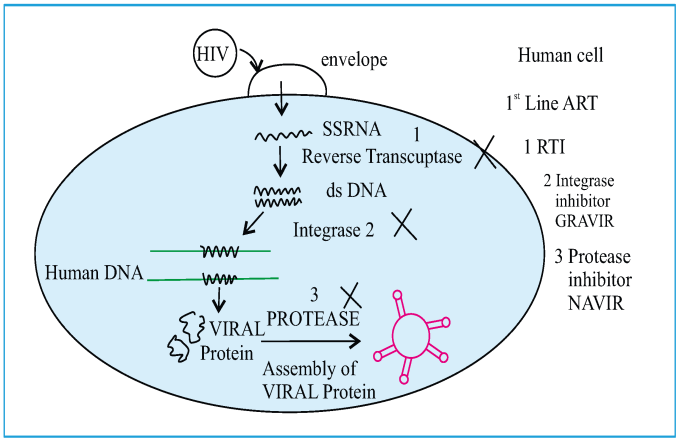
- Co receptors include
  - CCR-5
  - CCR-2

Entry Inhibitors

00:05:31

- Other Name: Fusion Inhibitors
- 2nd line antiretroviral therapy
  - Add on therapy in case of resistance in HIV

Glycoprotein 41 inhibitors	• Enfuvirtide • ROA: Injection • Active against HIV 1
Glycoprotein 120 Inhibitors	• Fostemsavir • ROA: Oral • Active against HIV 1
CD4+ Blocker	• Ibalizumab • Only monoclonal antibodies approved for HIV • ROA: Injection • Active against HIV 1
CCR-5 Blocker	• Present on the human cell • Drug: Maraviroc ○ Modification: Virciviroc • ROA: Oral • Active against HIV1 and HIV2
CCR 5 and CCR 2 blocker	• Drug: Cenicriviroc • ROA: Oral • Active against HIV1 and HIV2
Capsid inhibitor	• Drug: Lenacapavir • ROA: Injection • Active against HIV1 and HIV2



The envelope of HIV remains outside.

↓

Single-stranded RNA enters the human cell.

↓

RNA is converted into double-stranded DNA with the help of Reverse transcriptase enzyme

↓

Ds DNA attaches to the human DNA with the help of integrase enzyme.

↓

Formation of viral proteins

↓

Assembly of the viral proteins by protease enzyme

↓

Full-formed HIV

- 1st Line drugs include
  - Reverse transcriptase inhibitors

- Integrase inhibitors
  → Ends with the word -gravir-
- Protease inhibitors
  → Ends with the word -navir-

1. Reverse transcriptase Inhibitors (RTI)

- Inhibits the conversion of single-stranded RNA to dsDNA
- Other Name: RNA-dependent DNA polymerase
- Divided into three types based on their MOA
  - Nucleoside RTI (NRTI)
  - Nucleotide RTI (NtRTI)
  - Nonnucleoside RTI (NNRTI)

Nucleoside RTI (NRTI)	• Requires phosphorylation
	• Converts into fake nucleotides
	• Competitive inhibitors of reverse transcriptase enzyme
	• Active against HIV1 and HIV2
	• Drugs
	  ○ **Mnemonic:** DAZZELS
	  → **D - D**idanosine
	  → **A - A**bacavir
	  → **Z - Z**idovudine
	  → **Z - Z**alcitabine
	  → **E - E**mtricitabine PYQ: INICET 2022
	  → **L - L**amivudine
	  → **S - S**tavudine
	• Common side effect
	  ○ Bone marrow suppression
	  ○ Alopecia
	  ○ Myopathy
	  ○ Pancreatitis
	  ○ Peripheral neuropathy
	  ○ Hepatic steatosis
	  ○ Lipodystrophy: Obese, type 2DM
	  ○ Lactic acidosis: Inhibition of mitochondrial respiration
	• Zidovudine causes maximum risk of bone marrow suppression, alopecia, myopathy
	  ○ C/I: Severe anemia : Hb: <9 gm/dl
	  ○ Treatment: Erythropoietin injections
	• Didanosine causes maximum risk of pancreatitis
	• Stavudine causes maximum risk for
	  ○ Peripheral neuropathy
	  ○ Hepatic steatosis
	  ○ Lipodystrophy
	  ○ Lactic acidosis
	• Abacavir
	  ○ C/I: HLAB5701 positive. Test before administration to avoid severe allergic reaction.
	• Antagonistic NRTIs
	  ○ Causes most toxicity : Stavudine ; Didanosine ; Zalcitabine
	  ○ Cross-resistance : Lamivudine ; Emtricitabine
	  ○ Cross-resistance : Zidovudine ; Stavudine
	• Synergistic NRTIs (show synergism)
	  ○ Zidovudine with Lamivudine or emtricitabine
	  ○ Abacavir with Lamivudine or emtricitabine
	  ○ Lamivudine or emtricitabine is combined with Tenofovir

Nucleotide RTI (Nt-RTI)	• No phosphorylation
	• Competitive inhibitors of reverse transcriptase enzyme
	• Active against HIV1 and HIV2
	• Drug: Tenofovir
	  ○ DOC for HIV
	  ○ DOC for Hepatitis B virus
	  ○ Side effect: Nephrotoxic
	  ○ C/I: Renal disease (High creatinine), children
	  ○ Causes damage to PCT of nephron leads to phosphate loss
	  → Syndrome: Fanconi syndrome
	  → Hypophosphatemic rickets, osteoporosis
	• In renal failure and in children: Replace tenofovir with Zidovudine or Abacavir (Safe in renal failure)
	• Common drugs approved for HIV + HBV
	  ○ Tenofovir
	  ○ Lamivudine
	• Tenofovir: Available in two salts
	  ○ Tenofovir alafenamide: Longer acting
	  → Safe
	  ○ Tenofovir diproxil: Short-acting
	  → More toxic

Non nucleoside RTI (NNRTI)	• No phosphorylation PYQ: FMGE 2023
	• Noncompetitive inhibitors of reverse transcriptase enzyme
	• Active against HIV1
	• Have -vir- word in between
	• Drugs: **Mnemonic** NEED Dire Relief
	  ○ First generation
	  → Nevirapine: DOC in neonates
	  ▪ Neonatal prophylaxis from HIV+ mother (PTCT)
	  → Efavirenz
	  ○ Second generation NNRTI - Effective in the resistant cases of the first-generation
	  → Etravirine
	  → Delavirdine
	  → Doravirine
	  → Relpivirine
	• Side effects
	  ○ Hypersensitivity rashes
	  ○ Steven Johnson syndrome

Features	Nevirapine	Efavirenz
Metabolism	CYP3A4 substrate	CYP is not required
Rifampicin (CYP inducer)	• Increases the degradation (Not recommended) • Replaced with Rifabutin	Safely given

Side effects	Hepatotoxicity	• Neurotoxicity
		  ○ Psychosis
		  ○ Depression
		  ○ Peripheral neuropathy

Pregnancy	Safe	Safe

Important Information

- No HIV drug is contraindicated in pregnancy

1. Nucleoside reverse transcriptase and translocation inhibitor (NRTTI)

- Drug: Islatravir
  - ROA: Subdermal implants for HIV
  - Not approved in India

2. Integrase Inhibitors

- Inhibit DNA strand transfer to human DNA
- Ends with the word -gravir-
- Drugs: BCDER
  - **B**ictegravir
  - **C**abotegravir
  - **D**olutegravir (most used in India)
  - **E**lvitegravir
  - **R**altegravir

PYQ: INICET 2022

- All are oral drugs except Cabotegravir (IM), once every 3 months
- All are CYP3A4 substrates
  - Rifampicin reduces the effect of these drugs
    → Increase the dose of integrase inhibitor
- Side effects
  - Rashes
  - Steven Johnson syndrome: Epidermis of the skin is damaged
- Dolutegravir is safe pregnancy
  - Does not cause neural tube defects
- Dolutegravir + Rifampicin: Increase the dose of Dolutegravir

3. Protease Inhibitors

- Ends with the word -navir-
- MOA: Inhibits the assembly of viral proteins
  - Other Name: Packaging of viral proteins
- Drugs: RAFTISLAND
  - **R**itonavir
  - **A**mprenavir
  - **F**os-amprenavir
  - **T**ipranavir
  - **I**ndinavir
  - **S**aquinavir
  - **L**opinavir
  - **A**tazanavir
  - **N**elfinavir
  - **D**arunavir

PYQ: INICET 2021

- Common side effect: Produce lipodystrophy syndrome
- Lipodystrophy syndrome:

- Obesity, Breast hypertrophy
- Type 2 DM: Insulin resistance
- Dyslipidemia: Increase in LDL, TG
- Treatment: Tesamorelin
  → Recombinant GHrH

Specific side effects of protease Inhibitors

- Renal stone (Nephrolithiasis): Indinavir
- Hyperbilirubinemia: Atazanavir
  - Causes jaundice
- QT prolongation: Saquinavir
- Hypertension and intracranial hemorrhage: Tipranavir

Pharmacokinetics of Protease Inhibitors

- All are CYP3A4 substrates: Except Nelfinavir
  - Maximum CYP inhibitors: Ritonavir
    → Increases the toxicity of other drugs
- Simvastatin: Risk of Myopathy
- Midazolam: Causes Respiratory depression
  - Least CYP inhibiting action: Saquinavir

Boosted Protease Inhibitors

- Low dose ritonavir is combined with other protease inhibitor
  - Lopinavir
  - Darunavir
- Not combined with Nelfinavir

Ritonavir
↓
Inhibits the metabolism of other protease inhibitors
↓
Boost plasma levels

- New drug: Cobicistat
  - Derivative of Ritonavir
  - No antiviral activity
  - CYP3A4 inhibitor
  - Boost the plasma concentration of other drugs
    - → Atazanavir
    - → Darunavir
    - → Elvitegravir

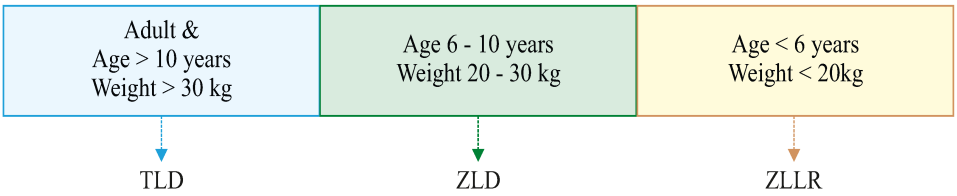
Miscellaneous drugs for HIV

Octreotide	• Somatostatin inhibitor • Treatment: Diarrhea in HIV patients • Reduces intestinal secretions
Crofelemer	• CFTR inhibitor ○ Cystic fibrosis transmembrane receptor inhibitor • New drug to treat diarrhea in HIV
Tesamorelin	• Recombinant GHRH • Treatment: Lipodystrophy syndrome

Treatment of HIV 01:02:30

- Guideline: NACP (National AIDS Control Program)
- Governing body: National AIDS control organization
- Give ART to all HIV-positive individuals
  - Irrespective of CD4 count
- No ART is contraindicated in pregnancy
- Minimum three drugs are recommended
  - At least from 2 different groups
    - → NRTI
    - → NtRTI
    - → NNRI
    - → Integrase Inhibitor
    - → Protease inhibitor
  - Lifelong treatment
- Given as a single fixed dose combination (3 drugs)
- Most preferred treatment (same treatment in pregnancy)
  - TLD: Tenofovir, Lamivudine and Dolutegravir
- Other options
  - TLLR: Tenofovir, Lamivudine, Lopinavir/Ritonavir
  - TEL: Tenofovir, Lamivudine, Efavirenz

HIV in Children



- Age: >10 years, weight >30 kgs: TLD (Tenofovir, Lamivudine and Dolutegravir)
- Age: 6-10 years, weight 20-30 kgs: ZLD (Zidovudine, Lamivudine and Dolutegravir)
  - Zidovudine
    → C/I: Anemia (Hb <9 gm/dl)
    → Replaced with Abacavir
    → Anemia in children: ALD, ALLR
- Dolutegravir: Avoided in children <6 years, weight <20kg
  - ZLLR (Zidovudine, Lamivudine, Lopinavir/Ritonavir)
- Tenofovir: Increased risk of rickets in children

Prophylaxis in a newborn infants

PYQ: AIIMS 2019

Low risk infants Maternal HIV after 32 weeks Having < 1000 copies of HIV
High risk infants Maternal HIV after 32 weeks Having > 1000 copies of HIV

- Breastfeeding is allowed
- Low-risk infants: Syrups of Nevirapine to neonate
  - Duration: 6 weeks
- High-risk infants: Syrups of Nevirapine + Zidovudine
  - Duration: 6 weeks
  - Syrups of Nevirapine + Zidovudine + Lamivudine
    → Duration: 12 weeks

Post-exposure Prophylaxis (PEP) for HIV

- Accidental contact with HIV-positive secretions
- Post exposure Prophylaxis: Within 2 hrs
- Duration: 28 days or 1 month
- Same 3-drug combination
  - Adult: TLD
  - Children: ZLD
  - Small children: ZLLR

TB and HIV coinfection

- Treat the opportunistic infection
- 1st antitubercular therapy
- After 2 weeks: ART

Hepatitis virus

01:15:47

Hepatitis A (HAV)	Self-limiting infection

Hepatitis B (HBV)	• Requires treatment
	• Treatment: Chronic active HBV
	• DOC: Reverse transcriptase inhibitors
	  ○ ROA: Oral
	  ○ Mnemonic: TECTAL
	  ○ First-line drugs
	  → Tenofovir
	  → Entacavir
	  ○ Second-line drugs
	  → Clevudine
	  → Telbivudine
	  → Adefovir
	  → Lamivudine
	• Common drugs for HBV and HCV: Interferon alpha
	  ○ ROA: Injection

Hepatitis C (HCV)	• Requires treatment
	  ○ Nonstructural protein inhibitors (DOC)
	  ○ Ribavirin
	  ○ Protease inhibitor
	  → Ritonavir
	  → Lopinavir
	• Common drugs for HBV and HCV: Interferon alpha
	  ○ ROA: Injection

Hepatitis D (HDV)	Causes infection along with HBV – superinfection/co-infection
Hepatitis E (HEV)	• Self-limiting infection • Pregnancy: Causes fulminant liver failure • DOC: Ribavirin

HBV

01:21:00

- **Mnemonic:** TECTAL
  - **T**enofovir
  - **E**ntacavir
  - **C**levudine
  - **T**elbivudine
  - **A**defovir
  - **L**amivudine

Tenofovir	• Most effective drug for Chronic Hepatitis B infection
	• Side effect: Nephrotoxic
	  ○ Phosphate loss (Fanconi syndrome)
	  → Hypophosphatemic rickets
	  → C/I: Children

Entacavir	• Resistant cases of tenofovir
Clevudine	-
Telbivudine	• Safe in renal failure
Adefovir	-
Lamivudine	• Resistance is common with HBV • Mutation: YMDD mutation

Important Information

- A common drug approved for both HBV and HCV is Interferon alpha
- Common drugs approved for both HBV and HIV are Tenofovir, Lamivudine
- A common drug approved for both RSV and HCV is Ribavirin

Interferon Alpha

- Treatment of HBV, HCV
- Interferon beta: Multiple sclerosis
- Interferon-gamma: Granulomatous disease
- Have two different forms
  - Interferon alpha 2A: Age >5 years
    → Once a week
  - Interferon beta 2A: Age >1 year
    → Thrice a week
- MOA: Inhibits viral replication at all steps
  - Main MOA: Inhibits the exit of the virus
- Side effects: Flu-like symptoms, hepatotoxicity, nephrotoxic, hypothyroidism
- PEG interferon: Long-acting
  - Poly ethylene glycol + Any drug

HCV 01:29:20

- DOC: Nonstructural inhibitors (Oral)
- It includes

PYQ: AIIMS 2019

• NS ¾A inhibitors ○ Functions as protease inhibitors ○ Ends with the word -previr- ○ Drugs include → Simeprevir → Boceprevir → Voxilaprevir → Telaprevir	• NS 5A inhibitors ○ Replication inhibitor ○ Ends with the word -Asvir- ○ They include → Ledipasvir → Ombitasvir → Velpatasvir → Elbasvir → Daclatasvir	• NS 5 B inhibitor ○ RNA polymerase inhibitor ○ Ends with the word -bruvir- ○ Drugs include → Sofosbuvir → Dasabuvir

Pan-genotyping regimens for HCV

- Have 7 genotypes
- Sofosbuvir + Velpatasvir: Oral for 12 weeks
  - 100% cure
- Sofosbuvir + Velpatasvir + Voxilaprevir: Oral for 12 weeks
- Glecaprevir + Pibrentasvir: Oral for 8 weeks

Sofosbuvir

- Inhibitors of NS 5 protein
- Excreted in urine by p-glycoprotein
- Rifampicin is an inducer of p-glycoprotein, hence reduces the effect of Sofosbuvir
- Side effects: Bradycardia

Ribavirin

- HCV: Interferon alpha + Ribavirin: Life long treatment
- Broad spectrum antiviral drug
- MOA: Inhibition of RNA polymerase
- Active against all RNA viruses
  - HCV
  - Respiratory syncytial virus
  - LASSA fever
  - Hemorrhagic fever
- Side effects: Aplastic anemia
- C/I: Pregnancy (Teratogenic)

Respiratory syncytial virus (RS)

01:38:35

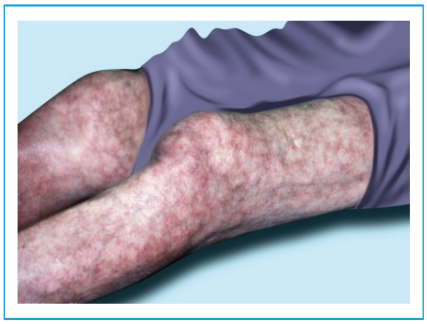
- Causes asthma-like illness: Bronchiolitis obliterans
- Occurrence: Newborn
  - Treat only children with pre-existing lung disease (Premature)
- DOC: Ribavirin
  - ROA: Aerosols
- DOC for prophylaxis: Palivizumab
- New drug: Nirsevimab

Influenza

01:41:41

- **Other Name:** Flu virus
- Has two types
  - M2 proton inhibitor
    - → M2 proton is present on the envelope of the influenza virus
    - → Inhibits the entry of virus
    - → Drug:
      - Amantadine: Used for Parkinson's disease
      - Rimantadine
    - → Effective against influenza A
  - Neuraminidase inhibitors

    PYQ: NEET PG 2019, 2022
    - → Inhibit the exit of the virus
    - → Drug:
      - Oseltamivir (Oral),
      - Zanamivir (Nasal drops),
      - Peramivir (Parenteral)
    - → DOC for influenza
    - → Effective in all types of influenza
      - H1N1: Swine flu
      - H5N1: Avian flu
- New drug for influenza A: Swine flu, Avian flu
  - DOC: Baloxavir
  - Cap endonuclease inhibitor
- Drug for influenza + Parkinson's: Amantadine
  - Side effects
    - → Livedo reticularis (due to vasodilation))



Herpes Virus

01:48:18

- DNA Viruses
- DOC: Acyclovir
  - Herpes simplex virus-1
  - Herpes simplex virus-2
  - Varicella zoster virus
  - Ebstein barr virus
    - → Side effects
      - Nephrotoxic
      - Neurotoxic
      - Not myelotoxic

- Cytomegalovirus: Largest
  - DOC: Ganciclovir

PYQ: FMGE 2023

  - Causes bone marrow suppression
  - Acyclovir: Not effective
    - → Side effects
      - Nephrotoxic
      - Neurotoxic
      - Myelotoxic

- Resistant to Acyclovir and Ganciclovir
  - Foscarnet
    - → Nephrotoxic, neurotoxic, not myelotoxic
  - Cidofovir
    - → Myelotoxic

New drugs for Cytomegalovirus

- DOC: Ganciclovir

Ganciclovir resistant cases

Fomivirsen	• RNA antisense strand
Letermovir	• Inhibits certain terminal complexes ○ Required for the replication of the virus
Maribavir	• Replication inhibitor

Acyclovir and Ganciclovir

- MOA: Acts as a nucleoside analogue that mimics guanosine
- In resistance cases, Foscarnet and Cidofovir are given
  - Do not require activation by viral thymidine kinase

PYQ: AIIMS 2019

Acyclovir and ganciclovir

↓

Phosphorylation

↓

Viral thymidine kinase enzyme

↓

Converted into Guanine 1 phosphate.

↓

Converted into Guanine 3 phosphate: Human thymidine enzyme.

↓

Attaches to the Herpes DNA

↓

Inhibition of DNA replication by inhibiting DNA polymerase

- Resistance is due to the mutations in viral thymidine kinase

Aciclovir Congeners	• ROA: Oral, IV, topical
	PYQ: FMGE 2020
	• Modified into Valaciclovir (longer acting)
	  ○ Pro drug: Converted to Aciclovir in the body
	  ○ Short-acting drug: Given 5 times a day
	  ○ Dose: 400 mg
	• Famciclovir: Oral pro-drug
	  ○ Active form: Penciclovir
	  → Available as an IV drug
	• Most effective drug for Varicella Zoster virus: Valaciclovir

Ganciclovir Congeners	• Only in IV injections
	• Causes pneumonia or CMV colitis
	• Also cause CMV retinitis
	  ○ Intravitreal injections of Ganciclovir
	• Valganciclovir: Prodrug of Ganciclovir
	  ○ Can be given orally

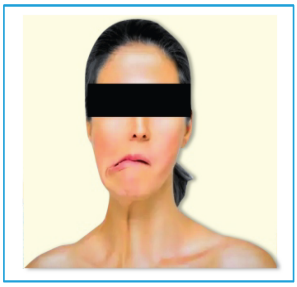
Foscarnet	• Inorganic phosphonate • Inhibits DNA replication • Give in the resistance cases of Acyclovir and Ganciclovir • ROA: Injections

Cidofovir	• Fake cytosine analogue
	• Inhibits DNA replication or DNA polymerase enzyme
	• Broad spectrum drug for all DNA virus
	  ○ Herpes
	  ○ Pox virus:
	  → Modified Cidofovir: Brencidofovir
	  ○ Polyomavirus
	  ○ Papillomavirus
	  ○ Adenovirus
	  ○ BTK virus
	• DOC for Respiratory papillomatosis: Cidofovir
	• DOC for Smallpox: Brencidofovir
	  ○ In case of bioterrorism
	• DOC for Monkeypox virus: Brencidofovir
	  ○ Another drug: Tecovirimat

Topical Drugs for Herpes

- Lips infection: Cheilitis
- Tongue infection: Glossitis
- Eye infection: Keratitis
- Available as
  - Eye drops
  - Creams/Lotions
- Drugs: **Mnemonic** VITA CD
  - **V**idarabine
  - **I**doxuridine
  - **T**rifluridine
  - **A**cyclovir (DOC)
  - **C**idofovir
  - **D**ocosanol (Alcohol)
- Others are preferred in Acyclovir-resistant cases

Bell's Palsy



- Facial nerve is paralyzed
- DOC: Prednisolone
  - Corticosteroids
- Suspect Herpes virus: Add
  - Acyclovir
  - Valaciclovir

PYQ: NEET PG 2022

Drugs approved by US FDA for

02:09:00

RNA polymerase inhibitors	• Remedesivir • Favipiravir • Molnupiravir • Nirmatrelvir
Antibody agonist spike protein	• Bebtelovimab • Sotrovimab • Cocktail mixture of MAB
Cytokine storm	• Tocilizumab: Inhibits IL-6 • Baricitinib: Inhibits JAK enzyme • Treatment for Rheumatoid Arthritis

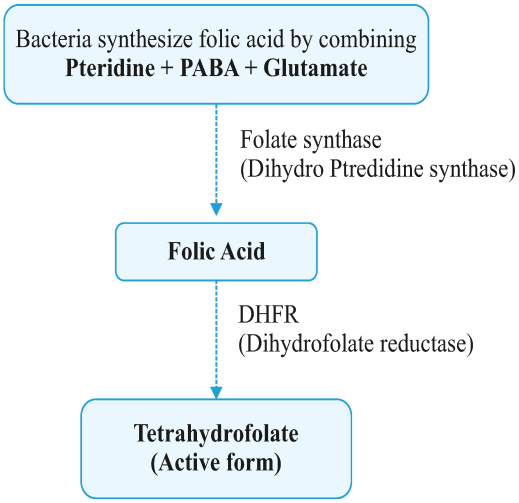
Mortality benefits in COVID 19	• Drugs include
	  ○ Corticosteroids
	  ○ Heparin: inhibits Disseminated intravascular coagulation
	  ○ Oxygen: Maximum mortality benefit

PYQ:INICET 2020

18 FOLIC ACID INHIBITORS

- **Also known as Anti-folate drugs**
- Folic Acid is needed for DNA, RNA, and protein synthesis in bacteria

Synthesis Process



00:02:17

Drugs that inhibit FOLATE synthase

- Sulfonamide
- Dapsone
- PAS

Drugs that inhibit DHFR

- Trimethoprim
- Proguanil
- Pyrimethamine
  - Adverse Effects of Drugs that inhibit DHFR – Megaloblastic Anemia
  - Methotrexate is a drug that inhibits DHFR in humans
  - With any drug that inhibits DHFR- a molecule named Folinic Acid (THF) is added to prevent megaloblastic anemia.

- All these drugs are bacteriostatic
- A combination of both drugs is a bactericidal combination

Important Information

- First drug for leprosy- Dapsone
- First drug for TB- PAS (Para-amino Salicylic acid)

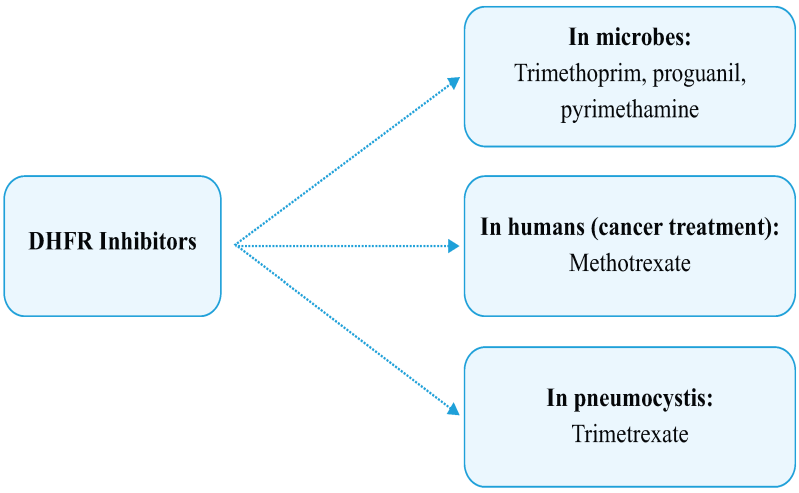
Q. Which drug (anti-microbial) requires folinic acid supplementation?

Ans: Any molecule that inhibits DHFR

- Trimethoprim
- Proguanil
- Pyrimethamine

Q. Folinic acid is an antidote for which anticancer drug?
Ans: Methotrexate (because this also inhibits DHFR)

00:07:25



- Along with these drugs Folinic acid is given.
- Folinic acid is also called Leucovorin/Citrovorum factor.

Bactericidal Combination

Mechanism: Sequential blockage of enzyme → Synergism (Supradditive)

- Sulfadoxine + Pyrimethamine + Folinic acid → Treat malaria
- Sulfadiazine + Pyrimethamine + Folinic acid → DOC for Toxoplasma gondii
- Sulfamethoxazole + Trimethoprim (also called Cotrimoxazole)

1. Cotrimoxazole 00:10:20

- **CO**mbination of **TRIM**ethoprim-Sulfameth**OXAZOLE**
- The ratio of Trimethoprim and Sulfamethoxazole is 1:5
- Also known as Trimethoprim + Sulfamethoxazole (TMP/SMX)

Cotrimoxazole is Drug of choice for

P	Pneumocystis jirovecii (Pneumonia in HIV- positive individuals)
I	Isospora / Cyclospora (diarrhea in HIV- positive individuals)
N	Nocardia
T	Typhoid prophylaxis
Beer	Burkholderia cepacia (mild: cotrimoxazole, severe: Carbapenems like meropenem)
C	Cystitis (bladder infections)

U	UTI
P	Prostatitis

2. Sulfonamides

00:13:30

Systemic (oral / IV)	Topical creams	Topical eye drops	Tropical oral (not absorbed)
• **Short acting :** Sulfacytine (shortest), sulfadiazine • **Intermediate – acting**: Sulfamethoxazole • **Long acting**: Sulfadoxine (longest)	• **Silver sulfadiazine (1%)** • Mafenide	• Silver sulfadiazine (10%) • Sulfacetamide	• Sulfasalazine (T/R Ulcerative Colitis, Rheumatoid Arthritis)

- Silver sulfadiazine is DOC in burns patient
- Lactic acidosis is a side effect of Mafenide and it is avoided in burn patient
- A combination of silver sulfadiazine (10%) and sulfacetamide is given as treatment for Keratitis (To protect corneal ulcers)

Sulfonamides

Mechanism of action
- Anti-folate drugs that inhibit dihydropteridine synthase
- Structure similar to PABA
- Competitive inhibitor

Pharmacokinetics
- SHIP drugs undergo Acetylation
- Slow acetylation causes high toxicity
- Therefore, common side effect → DLE (Drug induced Lupus erythematosus)

Adverse Effects
- **R**ashes / SJS (SULFA allergy)
- **A**plastic anemia (SULFA allergy)
- **S**low acetylators (SLE/ DLE)
- **H**emolysis in G6PD deficiency
- **A**ltered taste (Dysguesia)
- **B**ilirubin displacement from Albumin → Kernicterus
- **C**rystalluria (least risk in sulfisoxazole)

Contraindications
- Neonates
- 3rd trimester pregnancy
  - As they cause Kernicterus or brain damage in newborns

Q. In which infections are SULFONAMIDES not effective?
Ans. Not effective in Pus/Abscess infections because they contain a high amount of PABA

Q. Will you give Cotrimoxazole in the last trimester of pregnancy?
Ans. No, because Cotrimoxazole is contraindicated as it includes sulfonamides

3. Trimethoprim 00:25:15

- Inhibits DHFR
- **Side effect:** Megaloblastic anemia
- **Trimethoprim is Nephrotoxic**
  - They cause damage to the collecting duct of Nephrons, leading to RTA-4
  - Side effect: Hyperkalemia
- Treatment: Folinic acid for adverse effects

19 ANTIMICROBIALS: CHOICE, PROPERTIES AND RESISTANCE

Choice of Antimicrobials

Choice of Antibiotics in G6PD Deficiency

00:00:50

Safe (PCM)	Unsafe (MAD FANS Can)
Penicillins **C**ephalosporins **M**acrolides-erythromycin, Azithromycin Mefloquine is a safe antimalarial drug	**M**etronidazole **A**ntimalarials-Primaquine, proguanil, Quinine **D**apsone **F**luoroquinolones **A**spirin **N**itro drugs-Nitrofurantoin **S**ulphonamide **C**hloramphenicol

Choice of Antibiotics in Pregnancy

00:03:37

Safe (PCM)	Unsafe (FATS)
• **P**enicillins • **C**ephalosporins • **M**acrolides-Erythromycin, Azithromycin	• **F**luoroquinolones • **A**minoglycosides • **T**etracycline • **S**ulphonamides

- Fluoroquinolones and sulfonamides exhibit chelating properties, thus they cause bone and cartilage defects in the fetus.
- Aminoglycosides cause fetal ototoxicity.
- Sulfonamides cause kernicterus in the 3rd trimester of pregnancy.

Renal Safe Antibiotics

00:05:05

- These antibiotics "do not require dose reduction" in renal disease because they are excreted in bile

Totally	Tigecycline
Contraindicated	Cefoperazone
In	Isoniazid
R	Rifampicin
E	Erythromycin
N	Nafcillin
A	Azithromycin
L	Linezolid
Failure	Fluoroquinolones- Pefloxacin, Moxifloxacin, Trovafloxacin
Disease	Doxycycline

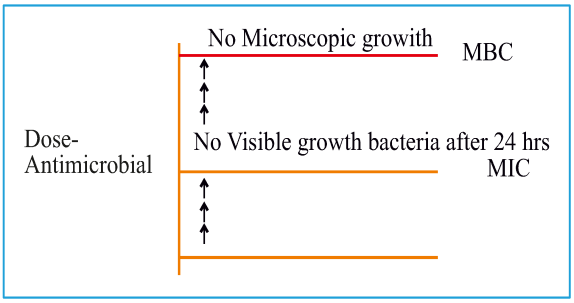
Bacteriostatic vs Bactericidal

00:07:25

Bacteriostatic (MS COLT)	Bactericidal (BANG Q RIP)
Macrolides **S**ulphonamides **C**hloramphenicol **O**xazolidinone (Linezolid) **L**incosamides (Clindamycin) **T**etracycline	**B**eta lactams (Penicillins, Cephalosporins, Carbepenems, Monobactams) **A**minoglycosides PYQ: INICET 2022 **N**itroimidazole (Metronidazole) **G**lycopeptides (Vancomycin) **Q**uinolones **R**ifampicin **P**olymyxin (colistin)

Why are certain antibiotics bactericidal or bacteriostatic?

00:09:00



To an agar plate or a broth with bacterial growth an antimicrobial is added

↓

The dose of antimicrobial is increased gradually

↓

At a certain concentration known as MIC (minimum inhibitory concentration), bacterial growth is not visible after 24 hrs

↓

The dose is further increased

↓

The concentration of antimicrobial that prevents microscopic growth is called as MBC(minimum bactericidal concentration)

- Based on this graph, drugs can be detected as bactericidal or bacteriostatic as follows,

Bacteriostatic	Bactericidal
• MIC<<<MBC • No complete killing of bacteria • Only growth is restricted • The remaining bacteria are killed by the immunity of the body	• MIC = MBC (near) • The complete killing of bacteria

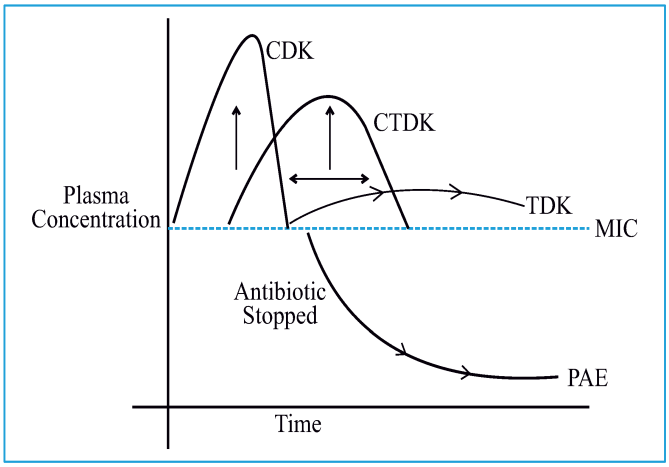
Q. Which drugs are used to treat infection in immunocompromised patients?

A. Bactericidal drugs E.g. Ciprofloxacin

Dosing of Antibiotics

00:15:05

- Also known as the pattern of killing by an antibiotic



- **CDK (concentration-dependent killing)**
  - Represents the Dose of antimicrobials above MIC that has good killing properties
  - Requires single high dose
- **TDK (time-dependent killing)**
  - Represents the long-term duration of antimicrobials to kill the bacteria
  - Requires multiple daily doses
- **CTDK - a combination of CDK and TDK**
  - CTDK is also known as area-dependent killing.
- **PAE- Post Antibiotic Effect**
  - Concentration falls below MIC but the drug continues to kill bacteria
  - PAE is defined as prolonged growth suppression of bacteria after brief exposure to an antibiotic.
  - This effect is due to our body's immunity.
  - **Advantage:** Total duration of therapy can be reduced.
  - **E.g. In TB, Rifampicin is given once a day as it shows concentration-dependent killing but in Leprosy Rifampicin is given once a month as it has a post-antibiotic effect.**

CDK + Long PAE	CDTK + Long PAE	TDK + Long PAE	TDK + Short PAE
• Metronidazole • Aminoglycoside • Rifampicin • Streptogramin (overall longest PAE)	• Daptomycin • Vancomycin • Fluoroquinolones	• Azithromycin • Telithromycin • Tetracycline	• Clindamycin • Penicillin • Erythromycin • Cephalosporin

Q. Which antibiotic shows TDK + long PAE

A. Rifampicin

B. Streptomycin

C. Penicillin

D. Fluoroquinolone

Ans. Fluoroquinolones because they show CTDK(CDK+TDK) + Long PAE

00:29:20

Types of antimicrobial resistance

Inherent resistance

Antimicrobials are never effective against that bacteria

E.g. Penicillin G is ineffective against E.coli

Metronidazole is ineffective against aerobic bacteria

Aminoglycoside is ineffective against anaerobic bacteria

Acquired resistance

With time, the bacteria has acquired resistance against antimicrobials

↓

Bacteria acquire resistance by acquiring a resistant gene

↓

The resistance gene is formed from a resistant protein.

↓

The resistance gene is acquired by three methods

Conjugation

One bacteria acquires a resistance gene from another bacteria via plasmid

E.g. Multidrug resistance to TB and Typhoid

Transduction

Bacteria acquires resistance gene from a virus called "bacteriophage".

E.g. MRSA (methicillin-resistant staphylococcus aureus)

Transformation

Bacteria acquire genes directly from the environment.

E.g. Pneumococci and Gonococci

00:34:30

Causes of Resistance

Drug influx

- The bacteria make changes in its cell wall protein due to which the drug cannot penetrate the cell wall.
- E.g. Cabapenem cannot enter pseudomonas.

Drug efflux

- The drug is thrown out of the bacteria by its special transporter.
- E.g. Antimalarials (chloroquine), Tetracyclines, Tigecycline.

Enzyme inactivation

- A bacterial enzyme called "beta-lactamase" degrades the antimicrobial drug
- E.g. Aminoglycosides, Beta-lactams (penicillins, Cephalosporins), Chloramphenicol

Mutation in target

- Bacteria produce different types of cell walls or cell membranes that prevents antimicrobials from binding to its target.
- E.g. MRSA (mutation in penicillin-binding protein-2A), Macrolide (mutation in 50s ribosome), Fluoroquinolones (mutation in DNA gyrase)

20 PULMONARY ARTERY HYPERTENSION

Idiopathic Pulmonary artery hypertension (PAH)

↓

Vasoconstriction in pulmonary artery

↓

Pulmonary pressure > 21 mm of Hg

↓

Right side part of the heart pumps blood with higher force

↓

Right ventricular hypertrophy

↓

Eventually damages heart

↓

Right heart failure

Pathophysiology — **Physiology** — 00:01:44

Endothelial dysfunction

Excess vasoconstrictive molecules
- Increased endothelin causes vasoconstriction

Reduce vasodilatory molecules
- Decreased Prostaglandin (PG) - I_2 and nitric oxide

PYQ: INICET2021

Role of Nitric Oxide

Reduced nitric oxide → Decreased stimulation of soluble guanylyl cyclase → Decreased cGMP → Vasoconstriction

↓

Degradation in the lungs by the enzyme phosphodiesterase (PDE) - 5

Drugs for PAH

00:05:45

- **Mnemonic-** PEPSI Coca Cola

PG-I_2 analogs

- **T** – Treprostinil
- **I** – Iloprost
- **E** – Epoprostenol
- **Route:** IV or inhalation (Not oral)

Endothelin receptors antagonist (drugs end with "Entan")

- Bosentan, Sitaxsentan: Blocks both ETA/ETB receptors
- Ambrisentan: Blocks ETA receptors
- **Route:** Given orally
- Contraindicated in pregnancy due to high teratogenicity

PDE 5 inhibitors

- Increased cGMP levels
- **Drugs**
  - **Sildenafil (Viagra): Also used for erectile dysfunction**
  - **Tadalafil**
- **Route:** Oral

Soluble guanylyl cyclase activators

- Increases cGMP levels
- **Drugs**
  - Riociguat
  - New drugs – Vericiguat for congestive heart failure

I_2 - Prostaglandin agonist

- Selexipag (Oral drug)

Continuous NO inhalation

- **Treatment of** Pulmonary artery hypertension (PAH)

Calcium channel blockers

- Amlodipine, nifedipine: **Pulmonary artery hypertension (PAH)**

DOC for Pulmonary artery hypertension (PAH)

- PG – I_2 analogs

Most effective for PAH (Grade 3)

- PG-I_2 analogs

Antihypertensives drugs for PAH

- Calcium channel blockers (CCB) – Systemic hypertension + PAH

1st drug to be started in mild PAH (Grade 1, 2)

Initial Treatment with Bosentan

↓

If not controlled

↓

Sildenafil or Riociguat

↓

If still not controlled

↓

PG-1_2 Injection

Vaso-Reactive Testing in PAH

00:13:42

Check for endothelial cells response by injecting IV adenosine/NO inhalation

Response → Vasoreactive positive PAH

- Vasodilation causing a decrease in > 10 mmHg
- <5% patients
- **DOC:** Calcium channel blockers (CCB)

No response →Vasoreactive negative PAH

- >95% patients
- DOC: Bosentan
  - Mild (Grade-I) and Moderate (Grade-II)
- DOC: PG-I_2 analogs
  - Severe (Grade-III)
- In Bosentan – resistant cases – PG-I_2 analogs are used.

21 ASTHMA

Drugs for Cough

00:00:05

- Cough- Protective reflex
- Has three types of drugs

Demulcents	• Inhibit the afferent or irritant impulse to the bronchus • Soothens the airway • These are lozenges, linctuses, glycerine
Expectorants	• Reduce mucus viscosity o Liquify the mucus o Expel the mucus as sputum • Recommended in productive or infective cough • Divided into two types of drugs o Mucokinetic- Increase the ciliary movements → Drug- Guaifenesin o Mucolytic- Liquify the mucus → MOA- Break the disulfide bond → Drugs include – Bromhexine (Pro drug) – Ambroxol (Active form) – N acetyl cysteine – Carbocisteine – Erdosteine
Anti-tussives	• Directly suppress the cough • Recommended in dry or allergic cough • Contraindication- Infective cough

Cough Mechanism

Sensory nerves arise from the bronchi of the lungs

↓

Enters the brain

↓

Cough impulses arise from the cough centers

- Drugs acting at lungs and nerves- Peripherally acting antitussives
- Drugs acting at CNS- Centrally acting antitussives

Peripherally acting antitussives	• Drugs include ○ Prenoxdiazine- Inhibits pulmonary stretch receptor ○ Local anesthetics- Blocks the afferent nerve supply → Benzocaine (Benzonatate) → Lignocaine
Centrally acting antitussives	• Act at CNS • Divided into three types (i) **Drugs acting on opioid receptors - Supress cough centre** 1. Morphine- Hydromorphone, oxymorphone 2. Codeine- Hydrocodone, oxycodone, pholcodine • Side effects ○ Addiction ○ Sedation ○ Constipation (ii) **Drugs not acting on opioid receptors (Non opioids)** 1. Dextromethorphan- Acts on glutamate receptor -NMDA antagonist 2. Noscapine- Sigma agonist • Advantages ○ No addiction (iii) **Antihistaminic drugs -** have peripheral action 1. Cetirizine 2. Promethazine 3. Fexofenadine • Advantage- No addiction

Cystic Fibrosis

00:13:12

Rare disorder

Pathophysiology

- It is an autosomal recessive disorder
- Genetic defect- CFTR channels

CFTR channels
↓
Secrete anions (Cl^-, HCO_3^-)

Drugs for Cystic Fibrosis

- Disease modifying therapy- Correct CFTR channels
- It prolongs the life expectancy of the patient

Drugs	Genetic Defects	Patient with CF
Lumacaftor or tezacaftor	F508 Deletion	Combination of three drugs are recommended- Tricafta
Ivacaftor	G551 Deletion	
Elexacaftor	Phe 508 Deletion	

Symptomatic Treatment

- Blockage of gland ducts - Dry eyes, mouth (Xerophthalmia, xerostomia)
  - Drugs - Pilocarpine, cevimeline
- Hard mucus
  - Drugs - Mucolytics
    - → N acetyl cysteine
    - → Erdosteine
    - → Carbocysteine
    - → Dornase alpha (Degrades DNA)
    - → Hypertonic saline
- Recurrent pneumonia- Pseudomonas pneumonia
  - Drugs - Inhalational antibiotics
    - → Tobramycin- Aminoglycoside
    - → Amikacin
    - → Colistin
    - → Aztreonam
- Chronic pancreatitis- Malabsorption can lead to chronic diarrhea
  - Drugs - Pancreatic enzyme replacement (Pancrezyme)

Asthma

00:21:31

- Type 1 hypersensitivity (Allergy)
- Inflammation leads to bronchoconstriction
- Symptoms
  - Dyspnoea
  - Chest pain
  - Wheeze

Treatment

Medicine

- Divided into two types
  - Antiinflammatory drugs
  - Bronchodilators

Anti-inflammatory drugs (Maintenance therapy)	• Used in prevention for chronic or persistent asthma • Prevent the recurrent attack if asthma (Secondary attack) • Drugs o Mnemonic- M Lo L C M → Mast cell stabilizers → LOX inhibitor → Leukotriene receptor antagonist → Corticosteroids → Monoclonal antibodies-(MAB)
Bronchodilators (Reliever therapy)	• Used during the acute attack of asthma • Drugs include o Mnemonic- BAT Man → **B**eta 2 agonists → **A**nticholinergic → **T**heophylline → **M**agnesium sulfate

Inflammation in Type 1 hypersensitivity

Antigen binds to the IgE antibody

↓

Mast cells release the various inflammatory mediators (Degranulation)

↓

LTC_4 and LTD_4 Acts on bronchus

↓

Acts on the receptor called CYS LT_1 receptor

↓

Bronchoconstriction/Asthma

↓

LTB_4, IL-5, IL-4 recruit white blood cells (eosinophils)

↓

Inflammation

- Location of IgE- Surface of mast cells
- Inflammatory mediators
  - Interleukins- IL-5, IL-4
  - Leukotrienes- LTB_4, LTC_4 and D_4
    - → Produced by 5-Lipoxygenase enzyme
    - → Other name for LTC_4 and D_4- Slow reacting substance of anaphylaxis (SRS-A)

Inflammatory mediators

Mast cell stabilizers	Inhibit the release of inflammatory mediators (-CROM-)
LOX inhibitor	Drug- Zileuton
Leukotriene receptor antagonist (LRA)	• Blocks CYS LT1 receptor of leukotriene • Drugs- (-Lukast-)
Corticosteroids	• Has broad mechanism of action • Other Name- Broad spectrum anti inflammatory drugs • DOC- Chronic or Persistent asthma
Monoclonal antibodies	• Blocks IgE antibody- Omalizumab • Blocks IL-5- Mepolizumab, Reslizumab, • Blocks IL-5 receptor- Benralizumab • Blocks IL-4- Dupilumab

Management of Asthma

Followed guidelines- Global initiative for asthma management (GINA) 2023

Acute attack of asthma

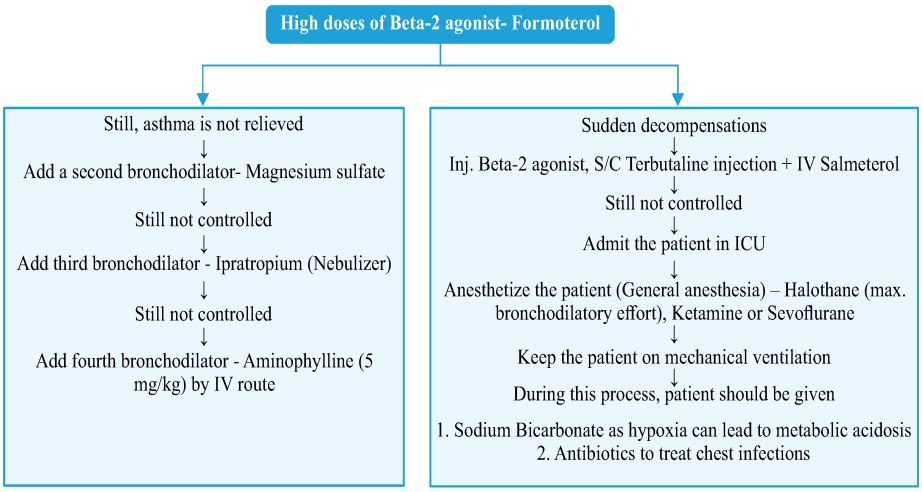
- Recommend bronchodilators
  - DOC- Beta 2 agonist
    - → Formoterol ± Budesonide
    - → Route - Inhalation

Status Asthmaticus / Acute Severe Asthma

- Acute attack of asthma not relieved by usual dose of β-2 agonist
- It is an emergency situation because patient may die due to hypoxia

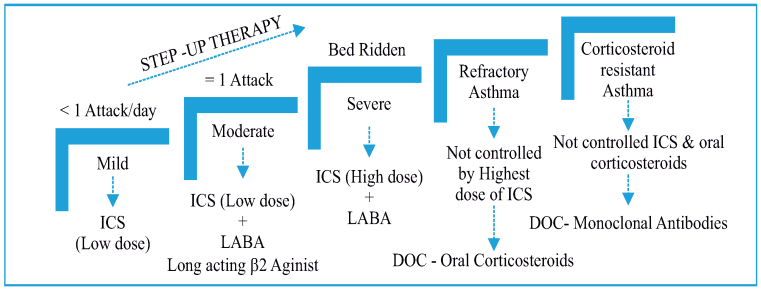
Management of Status asthmaticus

- Humidified oxygen to treat hypoxia
- Hydrocortisone- Treat inflammation
  - Route - IV
  - Dose- 100 mg stat
- High doses of β -2 agonist- Formoterol



Chronic or Persistent Asthma

00:40:21



<1 attack per day	• Well controlled- Replace inhalational corticosteroids with mast cell stabilizers (CROM) and leukotriene receptor antagonist (LUKAST) ○ Has steroid sparing action

Beta-2 Agonist

Mechanism of Action of Beta 2 Agonists

00:46:24

- Beta 2 receptors- GS type of G-protein coupled receptor

Acts on the beta 2 receptors located in bronchus
↓
Activate the adenylyl cyclase enzyme
↓
ATP is converted to cyclic AMP
↓
Levels of cyclic AMP increases in the bronchus
↓
Bronchodilation

- Cyclic AMP is degraded by phosphodiesterase 4
- Additional beneficial effects of stimulation of β-2 receptor - Increases mucus production in bronchus

Non-specific β-2 agonists	• Acts on β 2 and other receptors • Drugs include o Epinephrine- Acts on all α and β receptors → Epinephrine injections- DOC for Brittle asthma type 2 o Ephedrine- Acts on all alpha and β receptors o Isoprenaline- Acts on all types of beta receptors (β 1, 2 and 3)
Specific β 2 agonists	• Acts only on β 2 receptors • Divided into three types o SABA- Short acting β 2 agonist → Produce rapid affect → DOC for acute attack of asthma → Drugs – Salbutamol- Albuterol – Terbutaline (Active form) – Pirbuterol o LABA- Long acting beta 2 agonist → Produces for 12 hrs → It is given two times a day (BD) → Not given in acute attack of asthma → They are given to maintain bronchodilation in chronic asthma.' → Drugs: Salmeterol, Bambuterol (pro-drug) o Ultra-LABA → Produce effect for 24 hrs → It is given once a day (OD) → Not given in acute attack of asthma → They are given to maintain bronchodilation in chronic asthma → Mnemonic- IVOC – I- Indacaterol – V- Vilanterol – O- Olodaterol – C- Clenbuterol: Banned ▪ Anabolic effect
Formoterol	• Only β 2 agonist o Produce sudden affects o Maintain long term bronchodilation o Has both SABA + LABA properties • Single maintenance (chronic asthma) and reliever therapy (acute asthma) - SMART therapy
Enantiomers	• Levo or Ar' form -'Active form of β 2 agonists • Drugs include o Levo salbutamol o Arformoterol
Route of administration	• All β 2 agonists- Inhalational route or oral route • S/C injection- Terbutaline • IV injection- Salmeterol o Given in status asthmaticus

Adverse Effects of β 2 agonists

- **Mnemonic- 3H and 2T**
  - **H**ypoxia- Due to ventilation-perfusion mismatch
  - **H**yperglycemia- Breakdown of glycogen
  - **H**ypokalemia
  - **T**achycardia- Manifest as palpitations
  - **T**remors- Most common

Important Information

- Long term usage of LABA- Beta 2 receptors will stop responding
  - Desensitization of beta 2 receptors
  - Property is known as tachyphylaxis- Rapid tolerance
  - Treatment- Add corticosteroids
    → Regain the activity of beta 2 receptors

Mechanism of Action of Anticholinergic Drugs

01:02:53

Bronchus has an M_3 receptor (Acetylcholine)
↓
Stimulation of the receptor
↓
Bronchoconstriction
↓
Blockage of the receptor
↓
Bronchodilation

- Drugs include
  - Ipratropium
  - Tiotropium
  - Oxitropium
  - Umeclidinium
  - Aclidinium

Ipratropium	• Short acting muscarinic antagonist (SAMA) • Recommended in acute attack of asthma • Add on drug for beta 2 agonist in status asthmaticus
Tiotropium **Oxitropium** **Umeclidinium** **Aclidinium**	• Long acting muscarinic antagonist (LAMA) • Add on drug for beta 2 agonist in chronic COPD >> asthma • Route - Inhalational
Revefenacin **Glycopyrrolate**	• Newer drugs to treat chronic COPD • Add on drug for beta 2 agonist in chronic COPD and asthma

Side Effects

- Dry eyes/mouth
- Dry mucus
- Constipation
- Urinary retention

Normal Mechanism Paradoxical Bronchoconstriction by Ipratropium

Normal bronchus
↓
Vagus nerve
↓
Release acetylcholine that acts on the M_3 receptor
↓
Bronchoconstriction

- Ipratropium blocks the postsynaptic M_3 receptors on bronchi causing bronchodilation
- Paradoxical Bronchoconstriction by Ipratropium

(i) Ipratropium acts on certain receptors present on vagus nerve
↓
Blocks presynaptic M_2 receptor on vagus
↓
Increases the release of Ach
↓
Bronchoconstriction

(ii) Inhalation of ipratropium contains antibacterial preservatives like
- EDTA
- Benzalkonium chloride

- Not seen with Tiotropium

Theophylline 01:12:48

- It is a naturally occurring molecule, Non specfic PDE inhibitor
- It is a Natural- Methylxanthines
- Methylxanthines contains three molecules
  - Theophylline- Maximum present in Caffeine
    → Has peripheral action
    → Shows more action on bronchus
  - Caffeine- Maximum present in coffee
    → Has CNS action
  - Theobromine- Maximum present in chocolate

Caffeine	Treat migraine headache	Injections are given in apnea of newborn
Theophylline	• Bronchodilator ○ Used in the management of asthma and COPD	

Mechanism of Action of Theophylline

- Mnemonic- **PANCHI**
  - **P- P**hosphodiesterase 4 inhibitor
    → Increase in the levels of cAMP- Bronchodilation
  - **A**- Blocks Adenosine (A_1) receptor leads to bronchodilation
  - **N**- Inhibit NF kappa B
  - **C**- Calcium channel blocked
  - **H**- Causes Histone acetylation
    → Decrease the inflammation of IL-5, IL-4
  - **I**- Reduces the inflammation
- Main mechanism of action of Theophylline in asthma- Phosphodiesterase 4 inhibitor
- Specific PDE-4 inhibitors
  - Approved as bronchodilators in COPD
  - Drugs include
    → Roflumilast
    → Cilomilast
    → Ibudilast

Drugs

Theophylline	Given orally Insoluble in water
Etophylline	• Route: Oral, IV • Not given in inhalational route • Combination- Deriphyllin
Aminophylline	

Pharmacokinetic and Pharmacodynamic Properties of Theophylline

- Narrow therapeutic index drug
- Requires therapeutic drug monitoring
- Therapeutic range- 5 to 15 mcg/ml
- Metabolism- CYP 1 A2

Drugs reducing the effect of theophylline	Drugs increasing the effect of theophylline

• CYP enzyme inducers
• Drugs include
  ○ Griseofulvin
  ○ Phenobarbitone, Phenytoin
  ○ Rifampicin
  ○ Smoking and alcohol
	• Cyp inhibitor
	• Drugs include
	  ○ Ciprofloxacin
	  ○ Omeprazole
	  ○ Cimetidine
	  ○ Allopurinol
	  ○ Erythromycin

Theophylline toxicity

- Mnemonic- SUAGH
  - **S**eizures
  - **U**rination- Excessive diuresis
  - **A**rrhythmia

- GIT upset
  - → Nausea
  - → Vomiting
  - → Diarrhea
- Headache- Due to vasodilation

Seizures	Blockage of adenosine A_1 receptor in kidney and neuron
Urination	
GIT disturbances	Inhibition of phosphodiesterase enzyme in GIT and blood vessels
Headache	
Arrhythmias	• Blockage of adenosine A_1 receptor in heart • Inhibition of phosphodiesterase enzyme in heart

Magnesium Sulfate

01:26:47

- Blocks calcium channels leads to bronchodilation
- Route - IV
- Recommended in status asthmaticus
- Uses
  - Mnemonic- TABLETS
    - → Torsades De Pointes - DOC for arrhythmia
    - → Antacid- Magnesium hydroxide
    - → Given for calcium and barium poisoning
    - → Has a laxative effect (Treatment of constipation)
    - → Drug of choice for eclampsia
    - → Act as a tocolytic agent- Relaxes the uterus
    - → Given in status asthmaticus
- 1st sign of magnesium toxicity- Loss of deep tendon reflex / patellar reflex / knee jerk
  - Antidote- IV calcium gluconate

Anti Inflammatory Drugs

01:30:42

Mast cell stabilizers

- Drugs include
  - Nedocromyl
  - Chromoglycate
    - → Other Name- Cromolyin

MOA

Mast cells have sensory nerve endings © fibers)

↓

Release irritant molecule called capsaicin

↓

Activation of chloride channel

↓

Release of inflammatory mediators by mast cells

↓

Degranulation

- Mast cell stabilizers block C fibers, capsaicin, Cl- channels
- Route: Inhalation
- Has steroid sparing effect
- Reduce the dose of steroids in a patient
- Use- Chronic or persistent asthma, seasonal asthma (1 month before), exercise induced asthma (30 mins before)
  - DOC- Inhalational corticosteroid
  - Second choice- Mast cell stabilizers
- Not effective in acute attack of asthma
  - Not a bronchodilator

5-Lipoxygenase Inhibitor- Zileuton

- Reduce the synthesis of leukotriene
- Not used in asthma due to its hepatotoxicity property

Leukotriene Receptor Antagonist

- Blocks CYS LT_1 receptor of LT C_4/D_4
  - Levels of LT C_4/D_4 are increased
  - Recruit eosinophils
- Drugs include
  - Montelukast
  - Zafirlukast
  - Pranlukast
- Route: Oral, Topical

Uses

- Oral - Chronic asthma (Decrease dose of inhalational corticosteroid) } DOC- Inhalational corticosteroids
- Topical eye drops - Allergic conjunctivitis
- Aspirin induced asthma

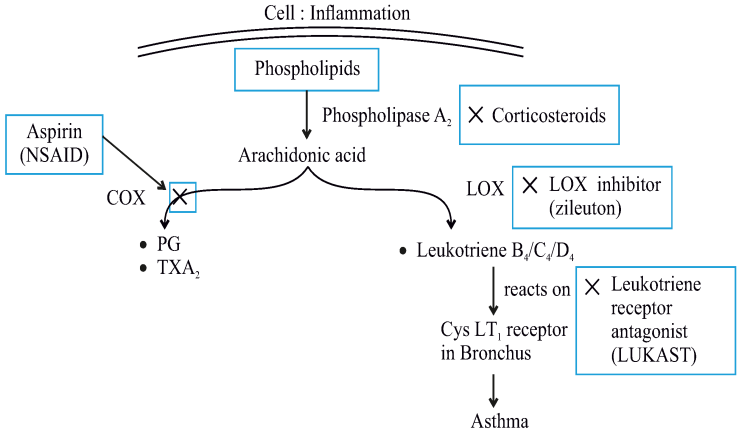
Side effects

- Churg Strauss syndrome
  - Other Name- Peripheral eosinophilia
  - Vasculitis

Aspirin Induced Asthma

01:39:13

- Phospholipase A_2 - Causes inflammation



- Treatment
  - Leukotriene receptor antagonist (LRA)
  - LUKAST type drugs
  - LOX inhibitor - Zileuton
  - Corticosteroids

DOC - Corticosteroids >>Leukotriene receptor antagonist (LRA) - LUKAST type drugs.

Corticosteroids

01:42:42

- Broad spectrum anti-inflammatory drugs
- Disadvantage- Not a bronchodilator

MOA

- Inhibits phospholipase A_2 enzyme
- Mast cell stabilizers
- Kill or reduce the lymphocytes, (Decreases IgE, IL-5 and IL-4), eosinophils

Types of Corticosteroids

Three types:

Inhalational Corticosteroids	• DOC- Chronic or persistent asthma • Drugs o Beclomethasone o Fluticasone- Most potent o Mometasone o Triamcinolone o Budesonide- Most commonly used o Ciclesonide
Oral Corticosteroids	• Recommended for refractory asthma • Drug- Prednisolone
IV Corticosteroids	• Recommended for status asthmaticus • Drug- Hydrocortisone (100 mg IV stat) and Dexamethasone

- Betamethasone- Not an Inhalational corticosteroid

Advantages of Inhalational Corticosteroid vs Oral Steroids

- Safe in pregnancy
- No risk of Cushing syndrome
- No risk of hypothalamic pituitary axis suppression or ACTH suppression

} Only in low dose ICS

Adverse Effects of Corticosteroids

- Hoarseness of voice- Dysphonia (most common)
- Characteristic side effect- Oral thrush
  - Candida infection of the fungus in mouth

MOA

Inhaler of corticosteroid
↓
Decreases immunity of the body
↓
Increase in the opportunistic infections like candida

- Treatment
  - → Localized candida- Local nystatin paint
  - → Pharyngeal and esophageal candidiasis - Oral fluconazole tablets
- Prevention-
  - → Do gargles and spit it out after taking ICS
  - → Use plastic spacer
  - → Use soft steroids- Ciclesonide
    - – Candida doesn't occur
    - – Pro drug
    - – Active- Inside lungs by esterase enzyme

Asthma Phenotypes

01:54:13

Seasonal Asthma	• DOC- ICS, mast cell stabilizers • Started 1 month before the season
Exercise or stress induced asthma	• DOC- ICS, mast cell stabilizers • Started 30 mins before exercise
Aspirin induced asthma	• DOC- ICS >> leukotriene antagonists, Zileuton
Brittle asthma	• Sudden worsening • Assessed through spirometer- Decreased peak expiratory flow rate • Divided into two types o Type 1- DOC is terbutaline S/C injection → Specific beta 2 agonist o Type 2- DOC is epinephrine S/C injection → Non-specific beta 2 agonist

Monoclonal antibodies in Asthma

01:56:28

- Recommended in corticosteroid resistant asthma
- Route: IV

Omalizumab	• Blocks IgE • Location- Surface of mast cells • Uses- Chronic asthma, urticaria, nasal polyps • Route: S/C injection once/month
Mepolizumab	• Route: S/C injection • Blocks IL-5 • Treat chronic asthma, Churg Strauss syndrome
Reslizumab	• Route:IV injection • Blocks IL-5 • Treat chronic asthma, Churg Strauss syndrome
Benralizumab	• Blocks IL-5 receptors
Dupilumab	• Blocks IL-4 receptors
Tezepelumab	• Newer drug • Blocks Thymic stromal lymphopoietin (TSL)

22 ACID PEPTIC DISEASE

Acid Peptic Disease

00:00:06

- 3 Diseases
  I. Hyperacidity
  II. Peptic ulcers
  III.GERD

Pathophysiology

Parietal cells of the stomach
↓
Responsible for HCl production
↓
Excess acid production - Hyperacidity
↓
Manifests as pain - Chest pain (heartburn)
↓
Can damage the stomach cells - Peptic ulcer
↓
HCl may go to esophagus
↓
Damage the cells of esophagus - GERD

II. Drugs

Class of Drugs	Examples
Acid suppressants • Reduces HCl production from parietal cells • Given on continuous basis (round the clock protection)	• PPI • H2 blockers • Antimuscarinic • Prostaglandins E1 (misoprostol)
Acid neutralizers • Directly neutralizes HCl in stomach lumen • Fastest acting • Given for prompt pain relief	Antacids
Ulcer protectives	• Sucralfate • Bismuth compounds
H pylori Infection	Antibiotics
Miscellaneous	• Antifoaming (Alginic acid) in GERD • Antiflatulence (Simethicone)

I. Hyperacidity - Acid suppressants

Medicine

On seeing food, the brain is stimulated
↓
Vagus nerve enters the stomach
↓
Releases Ach
↓
Activates M1 cells Present on histaminocytes of stomach
↓
Releases histamine
↓
Activates H2 receptor on stomach parietal cells
↓
Increases activity of H^+ K^+ ATPase pump (proton pump) PYQ: NEET PG 2020
↓
Produces HCl

- **Most effective drug:** PPI
- Vagus nerve sometimes Releases gastrin releasing peptide
  - Leads to gastrin secretion
  - Acts on CCK-2 receptor of parietal cells
  - **New drug in trial:** CCK-2 blocker (Netazepide)

	Anticholinergics	H2 receptor blockers	Proton pump inhibitors
Drugs	• Pirenzepine • Telenzepine	• Cimetidine • Ranitidine etc	• Omeprazole • Pantoprazole etc
Effectiveness	40 to 60%	60 to 80%	80 to 99%
Meal induced acid production	Reduces	Reduces	Reduces
Nocturnal or basal acid production	No effect	Reduces	Reduces

(I-c) Proton pump inhibitors

- Irreversible inhibitors of the Proton pump in the stomach
  - Suicide inhibitor
  - Hit and run drug
- **Drugs**
  - Dexrabeprazole (most potent)
  - Ilaprazole
  - Lansoprazole
  - Rabeprazole
  - Omeprazole PYQ: NEET PG 2020
  - Pantoprazole (least potent) - Requires maximum dose
  - Mnemonic: DILROPada
- All Drugs has equal efficacy
- Differ in potency (dose)

Important Information

- Potency of PPIs - Dex Rabeprazole > Ilaprazole > Lansoprazole > Rabeprazole > Omeprazole > Pantoprazole

- **Route of administration**
  - **Oral:** All PPIs
  - **Injectable:** IV/IM
  - Mnemonic: **PER**
    - → **P**antoprazole
    - → **E**s-omeprazole
    - → **R**abeprazole
- **Properties**
  - All are prodrugs
    - → Inactive drugs
    - → Active form: Sulfonamide moiety
  - **Half life:** 2 to 4 hours
    - → When the drug is given for 2 to 4 days
    - → Acid production Reduces even after stopping the drug for 2 to 4 days and resumes later
  - **Duration of action:** 2 to 4 days
  - **Fastest acting PPI:** Omeprazole
  - **Acid labile**
    - → First enter into intestine
    - → Then reach the blood
    - → And finally enter the parietal cells
    - → Inhibits Proton pump
    - → Enteric coating can protect from acid degradation
    - → H2 blockers: Acid resistance
  - Should be taken on an empty stomach
    - → Before 30 mins
    - → Maximum expression of H+K+ATPase in stomach
- **All PPIs metabolized by:** CYP2C19 enzyme
- **Maximum CYP inhibitor:** Omeprazole
- **Least CYP inhibitor:** Rabeprazole > Pantoprazole
- Omeprazole should never be given with Clopidogrel PYQ: FMGE 2023

Clopidogrel

- Pro drug
- Converted to active firm by CYP2C19
- If omeprazole is given along with clopidogrel
  - Blocks CYP2C19
  - Therefore, Inhibits antiplatelet action
- Rabeprazole or pantoprazole can be combined with clopidogrel
- **Pregnancy**
  - **Safest PPI:** Lansoprazole > all PPIs > omeprazole
  - Omeprazole should be avoided
- **Uses of PPIs**
  - Peptic ulcer due to any cause
    - → **H.pylori induced:** PPI + antibiotics
    - → NSAID induced
  - Bleeding specific ulcer or stomach bleed: I/V PPI (Reduce risk of bleeding).

III. GERD

- PPI + prokinetic (domperidone, mosapride etc)
- Prokinetics close the lower esophageal sphincter
  - **Aspiration Pneumonia:** Same as GERD
  - **Zollinger Ellison syndrome (gastrinoma)**
    → PPI + Octreotide
    → **PPI:** Inhibits acid secretion
    → Octreotide: Inhibits gastrin secretion
- **Adverse effect of PPI -** Occurs when there is chronic acid suppression
  - **Micronutrients deficiency**
    → Iron deficiency anemia
    → Calcium deficiency - Osteoporosis
    → Magnesium deficiency
    → Vitamin B12 deficiency - Megaloblastic anemia is not common
  - **Infections**
    → Community acquired pneumonia
    → Clostridium difficile diarrhea in intestine (pseudomembranous colitis)
    → Spontaneous bacterial peritonitis in intestine

Miscellaneous

- Gastrin levels increases: Gastrinoma (hypergastrinemia)
- Gastric polyps
- Gynecomastia - Due to Reduced testosterone by inhibiting CYP enzyme
- Impotence
- Menstrual irregularities in females
- Renal failure: Inhibition of Proton pump in nephron
- Alzheimer dementia: Inhibition of Proton pump in neuron

New PPIs

- Tenatoprazole: Also called reversible PPI
- Competitive blockers of K^+ site at H^+K^+ ATPase
  - Vonoprazan
  - Revaprazan
- Not metabolized by CYP2C19
- Approved for treatment of H. pylori infection

(I-b) H2 Blockers

- Competitive blocker of H2 receptor of histamine
- Cimetidine
  - Maximum CYP inhibiting action
  - Least potent drug
- Ranitidine
- Famotidine
  - Only non Competitive blocker of H2 receptor
- Roxatidine
- Nizatidine
  - Has maximum oral bioavailability
  - No CYP inhibiting action

- Lafutidine
  - Increase somatostatin levels
  - Reduces gastrin and HCl production

Side effects of cimetidine
- Gynecomastia and Impotence in males
- Menstrual irregularities in females
- Galactorrhea
  - Due to an increased in prolactin production
  - By blocking the D2 receptor in brain

- **Uses**
  - Same Uses like PPI
  - Preferred in stress ulcers

Acid Supressant Drugs- Prostaglandins E1 (Misoprostol)
- Oral drug
- **MOA**
  - Acts on EP receptor
  - Decreases HCl production
  - Increases bicarbonate and mucous production
- Used in the treatment of NSAID (aspirin) induced peptic ulcer
  - DOC is PPI

Miscellaneous
- Increases prostaglandin production in the stomach
- **Drugs**
  - Rebamipide
  - Ecabet
  - Carbenoxolone
    → Increases mineralocorticosteroids (aldosterone) production
    → Side effects
      – Hypertension
      – Hypokalemia

Antacids - Acid Supressant drugs
- Basic Drugs
- Directly neutralizes stomach Hcl
- Fastest acting drugs
- Prompt pain relief - Hyperacidity (heartburn)

Systemic Antacids
- Can be absorbed into blood - Hence , it has a lot of side effects
- **Sodium salts**
  - Sodium bicarbonate
    → Leads to the production of CO_2
    → Causes distention and perforation of the stomach
  - Sodium citrate: No CO_2 production
  - Fastest Antacids
  - Leads to hypertension or edema - Should be avoided in heart disease

- **Calcium salts**
  - Calcium bicarbonate or carbonate
  - When stopped - Maximum rebound acid secretion occurs
  - Milk alkali syndrome: Features are
    → Hypercalcemia
    → Metabolic alkalosis
    → Renal stones
  - Drug of choice in renal failure(also reduce the risk of osteporosis).
  - Causes constipation

Nonsystemic Antacids

- **Magnesium salts:** Magnesium hydroxide
  - Fast acting
  - Increased GIT motility
  - Causes diarrhea
- **Aluminum salts:** Aluminum Hydroxide
  - Slow acting
  - Reduce GIT motility
  - Causes constipation
  - Reduces phosphate absorption from GIT
  - Side effect: Osteoporosis
- **Both are combined:** MAGALDRATE
  - Has both fast and sustained action
  - Less effect on GI motility
  - Requires half dose of each

Ulcer Protectives

- Polymerize at acidic pH
- Precipitate with proteins over the ulcer - Protective covering
- Sucralfate
- Colloidal Bismuth salts
  - Subcitrate
  - Subsalicylate

Sucralfate Drugs

- Sucrose aluminum sulfate
- **Side effects**
  - Constipation
  - Osteoporosis
- **Drug interactions**
  - **Antacids**
    → Gap of 30 mins should be maintained
    → Because Antacids Increases GI pH (> 4)
    → But sucralfate to act need < 4 pH
    → Hence if given together Reduces the effect of sucralfate
  - **Avoid with food**
    → Maintain a gap of 1 hour
    → Because after meal pH is increased

- **Phenytoin, ranitidine and digoxin**
  - → Sucralfate Reduces GI motility
  - → Hence, it increases the residence time of the 3 drugs
  - → Increased risk of toxicity
  - → Gap of 120 mins should be maintained

Colloid Bismuth Salts

- Mnemonic: **3Ps**
- Protects stomach ulcers
- Prostaglandin synthesis increases
- Effective against pylori
- **Side effects**
  - Black tongue and black feces - Also occurs due to iron supplements
  - Bone: Osteoporosis
  - Rare side effect
    - → Reye's syndrome (hepatic encephalopathy)
    - → Main side effect of aspirin

Antibiotics against H.pylori

- Mnemonic: **CAMTL**
- **1st generation drugs** PYQ: FMGE 2021
  - **C**larithromycin
  - **A**moxicillin
  - **M**etronidazole (tinidazole, ornidazole)
- **2nd generation drugs**
  - **T**etracycline
  - **L**evofloxacin
- **New approved drugs** (3rd generation)
  - Rifabutin
  - Furazolidone
- **Guidelines for H.pylori**
  - 2 or more combinations of antibiotics should be given
  - Give PPI or H2 blocker
  - Duration of therapy: 10 to 14 days
- **Advantages of H.pylori treatment**
  - Decreased risk of recurrent Peptic ulcer
  - Decreased risk of GERD
  - Decreased risk of maltoma
  - No benefit in case of Barrett's esophagus

Anti H.pylori regimens PYQ: INICET 2020

- **Triple therapy:** PCM
  - PPI + Clarithromycin + Metronidazole
  - Given for 14 days, BD
- **Triple therapy:** PCA
  - PPI + Clarithromycin + Amoxicillin
  - Given for 14 days, BD

- **Quadruple therapy:** P-BMT
  - Used in clarithromycin resistant cases
  - PPI + Bismuth salts + Metronidazole + Tetracycline
  - Given for 14 days, BD

New Regimens of H.pylori

- Concomitant therapy: PCAM for 14 days
- Sequential therapy: PA then change to PCM
- Hybrid therapy: PA followed by PCAM for 7 days
- Levofloxacin based triple therapy: PAL
- Levofloxacin based sequential therapy: PA and then PML

Some Miscellaneous Drugs

- **Alginic acid**
  - Makes neutral covering over Hcl
  - Given in the treatment of GERD
- **Surfactant like molecules**
  - Drugs
    - → Simethicone and dimethicone
    - → Methylpolysiloxane
  - Burst bubbles in GIT
    - → In stomach reduces belching or burps - Antifoaming
    - → In intestine reduces flatulence - Antiflatulent

23 DRUGS FOR CONSTIPATION AND DIARRHEA

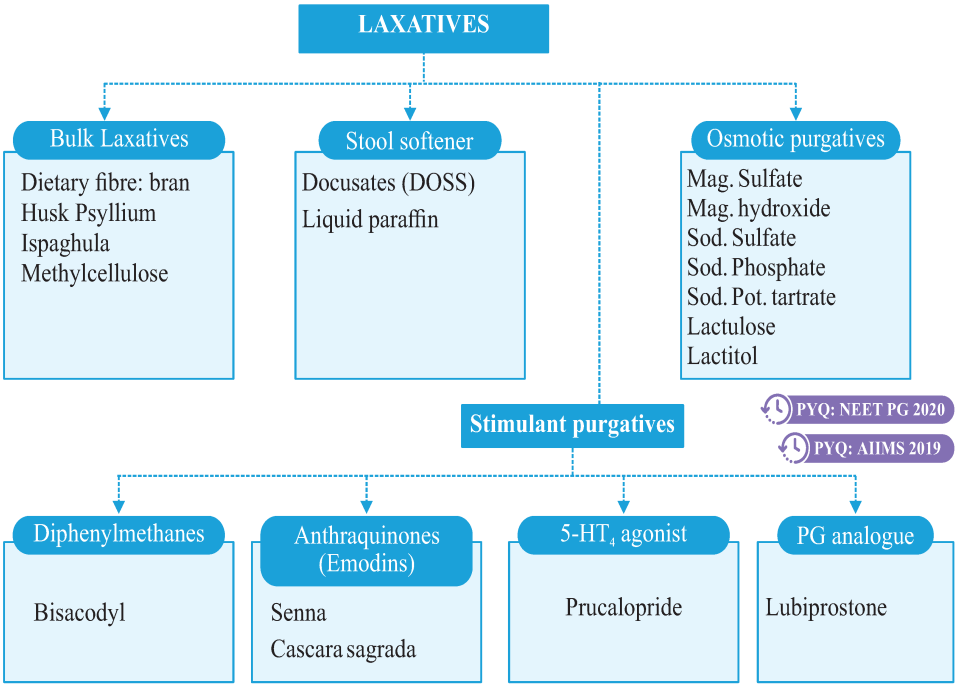
Definition

00:00:15

- Laxatives (mildly effective) - Expel formed stool
- Purgatives (strongly effective) - Expel watery stool

Drugs for Constipation

- Bulk laxatives
- Stimulant (irritant) laxatives
- Osmotic laxatives
- Stool softeners
- Chloride secretors
- Miscellaneous



Bulk laxatives

00:01:45

- Psyllium/ metamucil
- Bran
- Husk
- Methylcellulose
- Ispaghula/ isabgol

Mechanism of Action (MOA)

In a colon/ bowel they adsorb water on surface
↓
Bulk increases
↓
Causes stretching of colon
↓
Stimulation of sensory nerves
↓
Spontaneous contraction

Contraindication

Atonic colon (mega colon) - Paralytic ileus

Drug of Choice for:

- Idiopathic constipation
- Irritable bowel syndrome
- In pregnancy

Side effects

- Bulk laxatives are known as prebiotics
  - Increase the growth of colonic bacteria
  - Ammonia level increases
    - → Contraindicated in liver disease (Increase ammonia can enter and damage the brain)
    - → Contraindicated in GIT infections
- Flatulence
- Unpalatable

Stimulant (irritant) Laxatives

- Bisacodyl
- Senna
- Cascara

} Anthrol plant pigments

- Castor oil
- Prokinetics
  - Increases GIT motility
  - Prucalopride

Mechanism of Action (MOA)

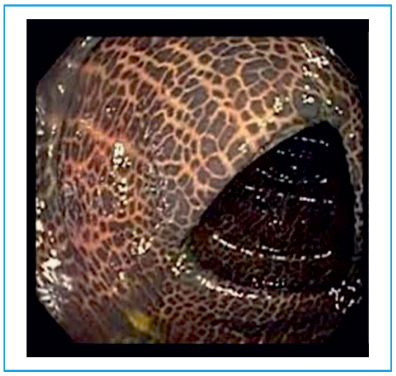
In bowel, they stimulate the muscles
↓
Causes active muscle contraction

Uses

- Resistant bulk
  - Idiopathic constipation
  - Irritable bowel syndrome
- Rapid bowel evacuation
  - Before surgery/USG/ Xray
    - → **DOC** saline purgatives/ osmotic laxative

Side effects

- Bisacodyl
  - Hypokalemia, Steven Johnson syndrome
- Senna/ cascara
  - Anthrol plant pigment(black)
    - → Causes melanosis coli



→ Blackening of colon

→ Avoided before colonoscopy

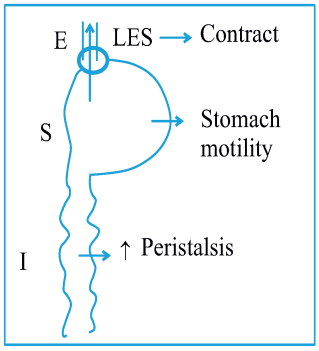
- Phenolphthalein: Carcinogenic risk

Contraindication:

- Pregnancy
  - Increased risk of abortion due to contractions

Prokinetics 00:12:39

- Increase GIT motility



Uses

- Constipation
- Gastroparesis
- GERD
  - Proton pump inhibitors+ prokinetics

Drugs

PYQ: AIIMS 2019

- $5HT_4$ agonist
  - Ends with **PRIDE**
  - Cisapride
  - Tegaserod
  - Mosapride
  - Renzapride
  - Itopride
  - Prucalopride

Important Information

Tegaserod and Cisapride (Banned)

- QT prolongation
- Torsades de pointus

- D_2 antagonist (Dopamine receptor blocker)
  - Domperidone
  - Levosulpiride
- Increases Ach levels
  - Neostigmine
  - Given in postoperative paralytic ileus
- Erythromycin / clarithromycin
  - Stimulate motility receptors in GIT
  - Used in Gastroparesis
  - Contraindicated in infant (<1 year): Hypertrophic pyloric stenosis
- Metoclopramide
  - $5HT_4$ agonist+ D_2 antagonist+ Raised Ach
  - It has antiemetic effect
  - Atropine (blocks Ach receptor)
    → Reduces effect of Metoclopramide

Domperidone (Antiemetic + prokinetic)	Metoclopramide (Antiemetic + prokinetic)
• D_2 antagonist	• D_2 antagonist, $5HT_4$ agonist, increases Ach levels
• Doesn't cross blood-brain barrier (BBB)	• Crosses blood-brain barrier (BBB)

• Do not cause drug-induced parkinsonism	• Causes drug-induced parkinsonism
	  ○ Muscle dystonia
	• Treated with anticholinergics
	  ○ Benzhexol

Osmotic Laxatives

00:23:33

- Saline purgatives (fastest acting)
  - Sodium phosphate / sulphate / picosulfate
- Magnesium salts
  - MgOH
  - Causes diarrhea
- Non-digestible sugars
  - Mannitol, sorbitol, glycerol
- PEG
  - Polyethylene glycol
- Lactulose
  - Laxative of choice in liver failure (Hepatic encephalopathy)
- Lactitol is also given in hepatic encephalopathy

MOA

Increases osmolarity of a colon
↓
Leads to watery secretion in colon
↓
Produces flushing/ irrigation
↓
Given for whole bowel irrigation

Uses

- Given before abdominal surgery / USG / Xray / Colonoscopy
- Most commonly used agent for bowel irrigation before colonoscopy is PEG (Polyethylene glycol)
- Given to expel dead worms and helminths

Hepatic Encephalopathy

- Cirrhosis of liver
- Liver converts ammonia to urea
- Ammonia comes from colonic bacteria
  - Enters brain
  - Leads to encephalopathy
- Mild symptoms
  - Lactulose
    → Reduces ammonia absorption from GIT
- Severe symptoms
  - GUT sterilization
    → Rifaximin (DOC)
    → Neomycin

Stool softener

00:30:49

- Docusate (DOSS)
- Paraffin wax
- Mineral oils
  - Not used now a days
  - Causes carcinogenesis, aspiration

MOA

Oily/ waxy substance
↓
Emulsify hard stools
↓
Soft stools pass without straining

Uses

- Given in pregnancy
- After abdominal surgery

Laxative of choice

- Laxative of choice in pregnancy
  - Bulk laxative
  - Docusate
- Laxative of choice in liver disease (hepatic encephalopathy)
  - Lactulose

New drugs

- Chloride Secretors:
  - Increases chloride secretion
    → Lubiprostone

→ PGE1 analog
→ Increases cAMP
- Sodium Secretors
→ Tenapanor
→ Inhibits Na/H antiporter

- All these are approved for constipation in irritable bowel syndrome

Miscellaneous Drugs for Constipation 00:35:52

- Neostigmine- Increases Ach - Used in post operative paralytic ileus
- Erthyromycin & Claritryomycin - Stimulates motilin receptors
- Opioid induced constipation
  - Opioid receptor antagonist: Alvimopan
    → Block opioid Mu receptor
  - Oral naloxone/ methyl naltrexone, etc.

Drugs for Diarrhea 00:37:52

- Fluid replacement
  - ORS
  - Ringer lactate
- Drugs (4A-2P)
  - Antibiotics
  - Anti motility
  - Anti secretory
  - Adsorbent
  - Probiotics
  - Prebiotics

Antibiotics 00:38:42

- Antibiotics: No Role (Mnemonic: PITCH)
  - **P**ancreatitis
  - **I**rritable Bowel Syndrome (IBS)
  - **T**ropical Sprue
  - **C**eliac Disease
  - **H**yperthyroidism
- Antibiotics: Given in Infected Diarrhea
  - Cholera
  - Clostridium difficile
  - Campylobacter
  - Protozoan Infections:
  - Amebiasis
  - Giardiasis

Anti motility 00:41:19

- Reduces intestinal peristalsis
- Given in non infective diarrhea
  → Avoided in infective diarrhea

Drugs

- Opioid agonist
  - Loperamide (DOC - Non-infective diarrhea) : Mu agonist, non addictive PYQ: FMGE 2022
    - → Don't cross BBB
    - → Drug induced: Irinotecan, Imatinib
  - Diphenoxylate: Mu agonist, addictive
    - → Combined with atropine: reduces addiction
  - Difenoxin
  - Eluxadolin/ Asimadoline: Kappa receptor agonist
  - Racecadotril
    - – Enkephalinase inhibitor
    - – Safest in children

Anti secretory: Reduces Na^+/ Cl^- secretion from colon 00:45:38

- Octreotide (DOC) for secretory diarrhea
  - → Carcinoid syndrome, VIPoma, HIV induced & cancer induced diarrhea
- Crofelemer
  - → Inhibits CFTR channel
  - → Used in HIV induced diarrhoea
- Alosetron
  - → Block $5HT_3$ receptor
  - → Given in diarrhea with irritable bowel syndrome (IBS)
  - → Given only in females
  - → C/I in males
    - – Increased risk of ischemic colitis

Adsorbent 00:48:10

- Absorbs excess water
- Bulk Laxatives - Psyillum,Ispagulla etc
  - Used in diarrhoea, constipation
- Bile acid binders
  - Cholestyramine(mucin) like action
  - Used in IBS

Prebiotics 00:49:46

- Increases bacterial growth
- Drugs: Bulk Laxatives

Important Information

Uses of Bulk Laxatives

- Diarrhea
- Constipation
- Prebiotics
- Dietary fibres

Probiotics

00:50:50

Important Information

Normal Gut Flora

- Bacteria
  - Lactobacillus
  - Bifidobacterium
  - Streptomyces
- Fungi
  - Sacharomyces

- Probiotics given in antibiotic induced diarrhoea
  - Clostridium difficile bacteria

Summary on Drugs Used in Irritable Bowel Syndrome

00:52:52

Constipation	Diarrhea	Abdominal pain	Gas or bloating
Psyllium / Husk/ methylcellulose (Bulk Laxatives) ↓	Antimotility: Loperamide ↓ Adsorbant:	Antispasmodics (SMR) Drotaverine Hyoscine ↓ (TCA) Tricyclic	Probiotics ↓ Dysbiosis Rifaximin ↓
Osmotic Laxatives (PEG. MGOH, sorbitol, lactulose) ↓ Chloride secretor Lubiprostone Linaclotide ↓ Prokinetic (Prucalopride)	Cholestyramine ↓ Alosetron in females	antidepressants SSRI: Fluoxetine	Low FODMAP diet

24 EMETICS, ANTIEMETICS, DRUGS FOR GALL STONES AND SHORT BOWEL SYNDROME

Miscellaneous Topics

- Emetics and antiemetics
- Drugs for gallstones
- Drugs for short bowel syndrome
- Pancreatic enzymes

Emetics and Antiemetics

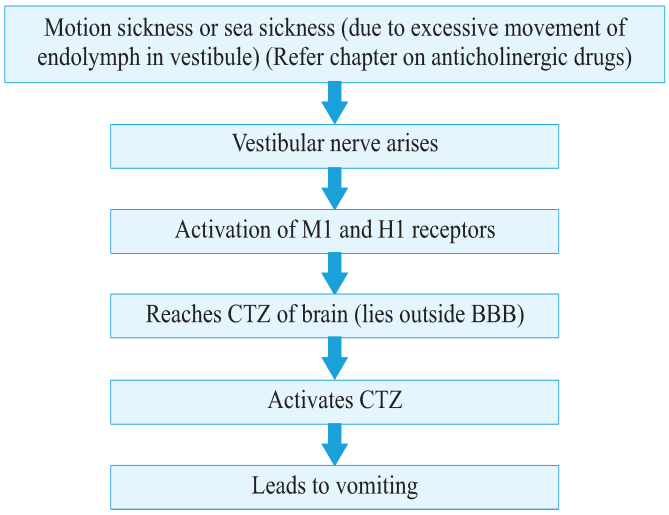
00:00:22

1. Emetics

- Induces vomiting
- **2 types**
  - Syrup of ipecac - Derived from plant called ipecacuana
    - → Active component: Emetin
    - → Oral
  - **Apomorphine**
    - → Injections
    - → Also used in parkinson's disease and erectile dysfunction
- Both drugs activate dopamine in CTZ - Leads to vomiting
- Used in the treatment of oral poisoning
- **Contraindicated in poisoning of**
  - Corrosive (acids or alkali): May cause perforation of stomach and esophagus
  - CNS stimulants (cocaine or amphetamine): Leads to seizures
  - Kerosene or petroleum - Risk of aspiration pneumonia
  - Unconscious patients - Risk of aspiration pneumonia
  - Opioid or morphine - Emetics are not effective

2. Antiemetics

- Suppress vomiting



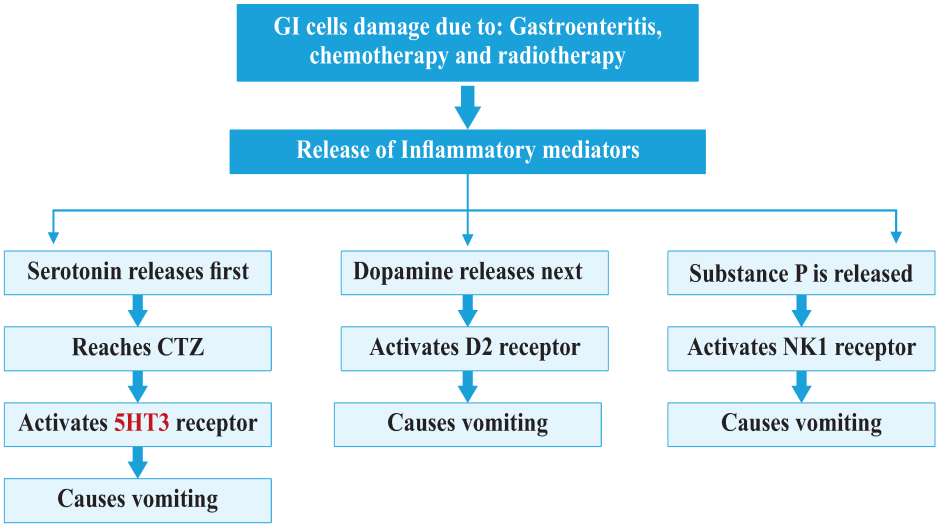
Drugs for motion sickness and sea sickness

- **Anticholinergic drugs**
  - Blocks M1 receptor
  - Hyoscine (scopolamine)

- **Antihistaminic drugs**
- Blocks H1 receptor
- 1st generation drugs preferred - Can cross BBB
- Diphenhydramine
- Promethazine
- Cyclizine
- Meclizine
- Cinnarizine

Vomiting due to excessive fear

- Anticipatory vomiting
- Lorazepam is a benzodiazepine are used



Important Information

- Cannabinoid is released from damaged GI cells
- Activates CB1 cells
- Decreases vomiting

Chemotherapy induced Nausea and vomiting

- **5HT3 receptor antagonists**
  - Called setrons
  - DOC:
    - → Chemotherapy induced nausea and vomiting
    - → Radiotherapy induced nausea and vomiting
    - → Gastroenteritis
  - **Drugs include**
    - → Ondansetron
    - → Granisetron
    - → Tropisetron
    - → Palonosetron
  - **Side effect:** Constipation
  - 1st 3 drugs effective in early phase (< 24 hrs)
  - **Delayed phase of CINV:** If vomiting continue > 24 hrs

PYQ: FMGE 2021

PYQ: NEET PG 2019

- **NK1 receptor antagonist**
  - Given in delayed phase
  - End with pitant
  - **Drugs**
    - → Apripitant
    - → Fos-Apripitant (injectable)
    - → Netupitant
    - → Rolapitant
  - **Side effect:** Diarrhea
- **CB1 Agonist**
  - Contains -nabi- word
  - Drugs
    - → Dronabinol
    - → Nabilone
  - Stimulates appetite
- **Dexamethasone:** Reduces release of Inflammatory mediators
- **D2 antagonist**
  - **Domperidone:** Treats levodopa induced vomiting
  - Metoclopramide (refer prokinetic drug chapter) PYQ: FMGE 2023
  - **Antipsychotics** PYQ: NEET PG 2022
    - → **Prochlorperazine:** DOC for violent vomiting
    - → Chlorpromazine
    - → Amisulpiride or levosulpiride
    - → Also used in treatment of vomiting due to migraine

Drugs for Dissolving GallStones 00:17:42

Statins

- Reduces cholesterol production
- Atorvastatin and rosuvastatin

Bile acids

- Reduces surface tension
- **2 types**
  - **Chenodeoxycholic acid**
    - → Decreases cholesterol synthesis in liver
    - → Increases LDL
  - **Ursodeoxycholic acid -** DOC for dissolving gallstones
    - → Decreases cholesterol absorption from intestine
    - → Decreases LDL
    - → Also used in the treatment of primary biliary cirrhosis
    - → New drug: Obitocholic acid

Drugs for Short Bowel Syndrome 00:20:35

- If a part of large intestine is removed - Short bowel syndrome
- Leads to malabsorption causing chronic diarrhea
- **3 new drugs (Mnemonic: GOT)**
  - **Growth hormone**
    - → Increases IGF-1
    - → Increases growth of bowel cells
    - → Therefore, increases absorption

- **Octreotide**
  - → Reduces malabsorptive diarrhea or diarrhea
  - → Decreases intestinal secretions
- **Teduglutide** PYQ: NEET PG 2019
  - → Recombinant form of GLP-2 analogue
  - → Increases IGF-1

Pancreatic Enzyme Replacement 00:23:20

- **Used in**
  - Treatment of chronic pancreatitis or
  - After pancreatectomy
  - Cystic fibrosis
- Pancreatic enzyme deficiency leads to chronic diarrhea due to malabsorption
- **Drug:** Pancreazyme
  - This drug is combination of enzymes- Lipase + trypsin
  - Lipase >>> trypsin
  - **Lipase:** Reduces malabsorption or steatorrhea
  - **Trypsin:** Relieves pain of chronic pancreatitis

25 ANTI-PLATELETS AND PRO-PLATELET DRUGS

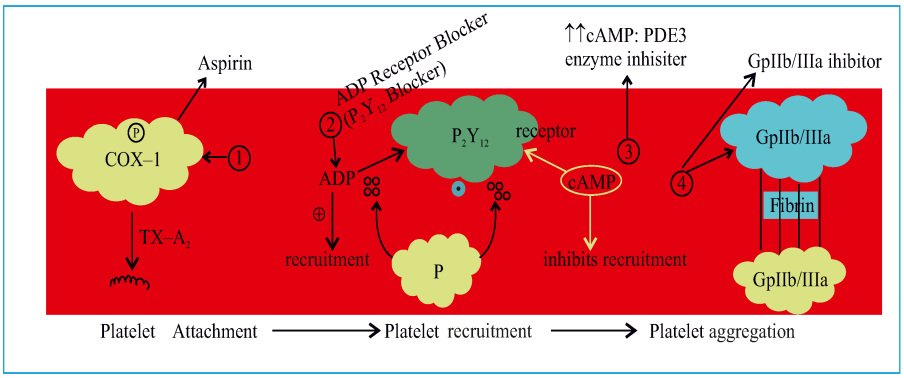
	Action	Monitoring
Antiplatelets	Prevent the formation of platelet-rich thrombus	• Effect is monitored by bleeding time ○ Increase in bleeding time: Antiplatelet toxicity
Anticoagulants	Prevent the formation of fibrin-rich thrombus	• Increases clotting time ○ PT (Prothrombin time) ○ aPTT (Activated Partial Thromboplastin Time)
Fibrinolytic (Thrombolytics) PYQ: NEET PG 2023	• Degrade the deposited fibrin • Lyse, remove or dissolve a clot	• D-Dimer monitors effect PYQ: NEET PG 2023 ○ Degradation product of fibrin ○ High amount indicates more fibrin degradation

Antiplatelets

00:04:05

- Prevent platelet aggregation

Normal action of platelet



Platelet contains COX 1 enzyme

↓

Produces thromboxane A_2

↓

Causes platelet attachment on blood vessel

↓

Attached platelets releases chemicals like ADP

cAMP is also released which inhibits platelet recruitment

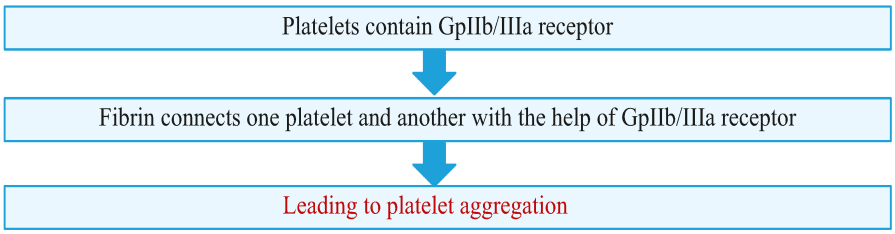
↓

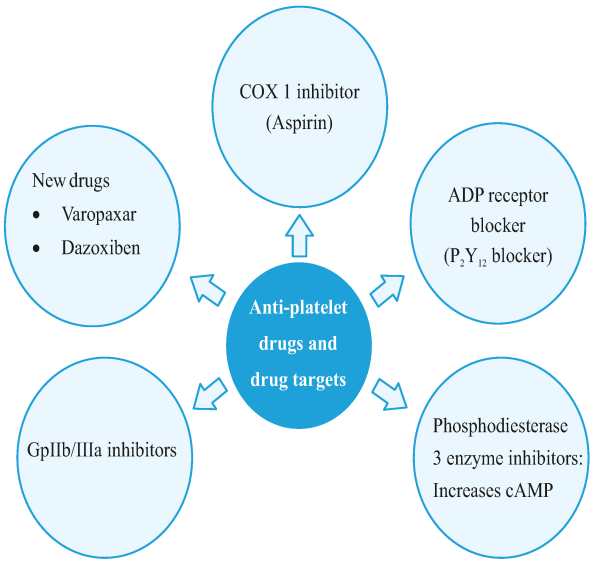
ADP attaches to the P_2Y_{12} receptor on other platelets

↓

Causes recruitment of more platelets

↓





Uses

- To treat MI (Acute coronary syndrome)
- Ischemic stroke or transient ischemic attack
- Peripheral vascular disease
  - Intermittent claudication – Seen in Buerger's disease
- DOC in all above-mentioned diseases: Aspirin
- Dual antiplatelet therapy (DAPT)
  - **Aspirin + other add-on drug:** Dual antiplatelet therapy

Aspirin

00:15:25

PYQ: NEET PG 2023

Other names

- Irreversible COX inhibitor (suicide inhibitor /Hit and run drug)
- Binds with covalent bonds.

Mechanism of action

Inhibits COX-1 enzyme in platelets → Reduces production of TxA_2 → Inhibits platelet attachment

Uses

- Drug of choice (DOC) for the following conditions:
  - MI (Myocardial infarction)
  - Stroke
  - Buerger's disease

Dose

- Antiplatelet dose of aspirin: 40 to 325 mg
  - **Acute MI and stroke:** 325 mg
    → Oral
  - Secondary prevention: 75 to 100 mg
    → Oral
    → To prevent a secondary attack (recurrence), lifelong aspirin should be taken.

Side effects

- Increases bleeding time
- Peptic ulcers or stomach ulcers
  - Treatment (DOC): Proton Pump Inhibitors (PPI) (-prazole)> misoprostol.

Precaution

- Should be stopped 7 days before surgery
  - It gives time for new platelet formation
  - This helps prevent excess blood loss during surgery

Contraindication

- Breastfeeding (may lead to Reye's syndrome in neonate)

ADP Receptor or P_2Y_{12} Blocker

00:22:25

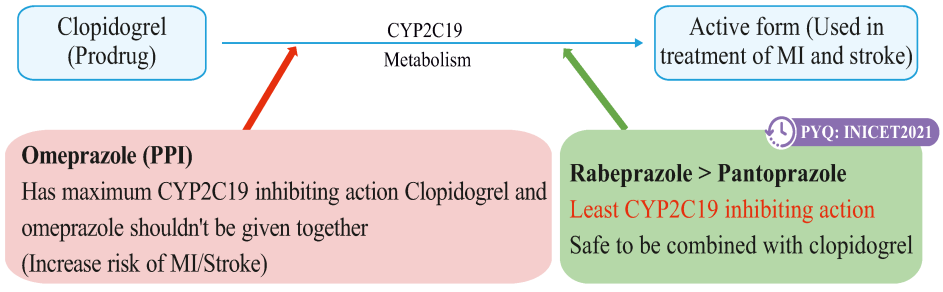
Irreversible blockers	Reversible blockers
• Ticlopidine • Clopidogrel • Prasugrel • All are prodrugs (Inactive drugs)	• Ticagrelor • Cangrelor – IV drug (used during Percutaneous transluminal coronary angioplasty (PTCA) • Active drugs

- These drugs are used as add-on drugs to aspirin (Dual antiplatelet therapy) and produce synergistic action.

Uses

- Ticlopidine and clopidogrel given in both MI and stroke
- **Prasugrel, ticagrelor and cangrelor**
  - Used only in MI
  - Contraindicated in stroke
  - Because these three drugs, increase the risk of severe bleeding (increasing risk of hemorrhagic stroke)

Pharmacokinetics



- **Side effects ADP/P_2Y_{12} receptor blockers**
  - Diarrhea (most common)
  - Thrombotic thrombocytopenic Purpura
    → When the drug binds to the ADP receptor, platelets become antigenic, leading to the production of antibodies against the platelets. This process results in platelet destruction and the blockage of blood vessels.
  - **Ticlopidine**
    → Causes bone marrow suppression (Agranulocytosis)
    → Rarely used

Phosphodiesterase 3 Inhibitors

00:32:18

Mechanism of action

- Increases cAMP and inhibits platelet recruitment

Drugs include

- **Pentoxifylline**
  - Rheological agent (improves blood circulation)
  - Improves elasticity of RBC
- **Dipyridamole**
  - 1st developed as an antianginal drug
  - Banned, as it causes coronary steal syndrome
- **Cilostazol**

These drugs are used as an add -on drug to aspirin in cases of Stroke and Buerger's disease.

Contraindication

- **Myocardial infarction**
  - Because it may inhibit PDE3 in heart
  - Increases cAMP causing cardiac stimulation which in turn increases heart rate and O_2 demand

Side effects

- Headache (most common)
- Hypotension

Buerger's disease

- The patient has intermittent claudication
- Cilostazol is commonly used
- If the condition is severe
  - The patient feels pain even at rest
  - Pentoxifylline injections are preferred

GpIIb/IIIa inhibitors

00:37:42

Also known as

- Antiaggregant drugs
- Anti-integrin drugs-Because GpIIb/IIIa is an integrin molecule

Drugs

Mnemonic: EAT

- **Eptifibatide**-Peptide molecule
- **Abciximab**
  - Monoclonal antibody
  - Safe in renal failure
  - Has additional immunosuppressive action
  - $T_{1/2}$: 30 mins
- **Tirofiban**-Non -peptide

Uses

- Eptifibatide, Abciximab and Tirofiban are given by IV only
- **Acute attack of MI or stroke**
- Stent replacement (Percutaneous transluminal coronary angioplasty)

New Antiplatelet drugs

00:41:36

Vorapaxar	Dazoxiben
• PAR inhibitor (Protease activating receptor) • PAR receptor on platelets is a receptor of thrombin ○ No attachment of thrombin on blocking these receptors leads to no platelet aggregation • Recently approved as an add-on drug to aspirin in MI	• Thromboxane A_2 synthase inhibitor • Under trial for MI • Prostaglandin G_2 is present inside the platelet and is produced from arachidonic acid by the COX-1 enzyme. • PG-G_2 converts to TxA_2 by thromboxane A2 synthase. • Aspirin blocks COX-1

Pro-Platelet Drugs

00:45:03

- Increases platelet count

Liver
↓
Synthesize thrombopoietin
↓
Reaches the bone
↓
In bone marrow megakaryocytes are present
↓
Thrombopoietin binds to its receptor on megakaryocyte
↓
Platelet production

- **IL-11:** Causes platelet formation by binding to megakaryocyte
- **Drugs**

Romiplostim	• Recombinant form of thrombopoietin • Given as a subcutaneous injection • Treatment of idiopathic thrombocytopenic purpura (ITP)
Eltrombopag	• Thrombopoietin receptor agonist • Present on megakaryocyte • Oral drug • Treatment of ITP and chronic liver disease • Similar drugs – Avatrombopag, Lusutrombopag
Oprelvekin	• Recombinant from of IL-11 • Given as a subcutaneous injection PYQ: NEET PG 2023 • DOC in chemotherapy-induced thrombocytopenia

- **Idiopathic Thrombocytopenic Purpura (ITP)**
  - ITP increases in immunity of the body and damages platelets
  - New drug for ITP: Fostamatinib
    - → Tyrosine kinase inhibitor
    - → Tyrosine kinase receptors are immunity receptors
    - → Hence, reduces the immune action finally reducing platelet damage

26 ORAL ANTICOAGULANTS

- Prevents deposition of fibrin
- Fibrin causes blockage of blood vessels.

Anticoagulants Uses

00:00:38

DVT (Deep Vein Thrombosis) / PE (Pulmonary Embolism)

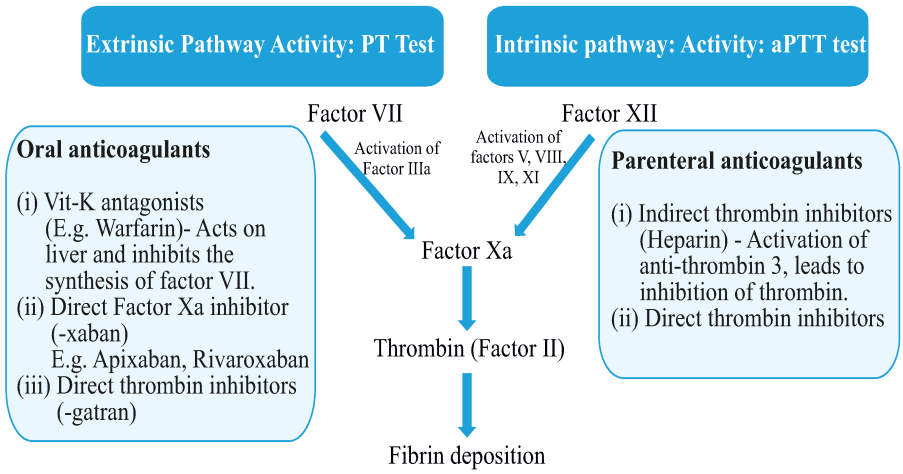
- Reduced blood flow and movement of the legs (immobility) cause fibrin deposition and form fibrin thrombus, leading to DVT (deep vein thrombosis).
- An emboli from the fibrin thrombus could cause blockage in the blood vessels of the lungs leading to pulmonary embolization .
- Examples of immobile patients: ICU patients, After knee/hip surgery

Transient ischemic attack/Ischemic stroke

- Ineffective contraction of atria (atrial fibrillation) and closure of the mitral valve (mitral stenosis) leads to fibrin deposition in the left atria.
- An emboli from this thrombus could enter the circulation and block blood vessels of the brain leading to transient ischemic attack/ischemic stroke.
- Treated by anticoagulant drugs.

Disseminated intravascular coagulation (DIC)

- Fibrinogen (the inactive form of fibrin) present in the blood is converted to fibrin by the clotting pathway.
- Over-activation of the clotting pathway leads to disseminated intravascular coagulation.
- Causes of DIC
  - Infection or sepsis – most common cause
  - Amniotic fluid or placental products in maternal circulation due to Abruptio placentae
  - Cancer induced thrombosis
  - Catheter induced thrombosis
  - Mechanical /artificial heart valves (treated with lifelong oral Warfarin)
- DIC has a high mortality
- DOC: IV Heparin



Important Information

- Direct thrombin inhibitors are both oral and parenteral drugs

Anticoagulant drugs

00:13:55

Vitamin K Antagonists	Direct factor Xa inhibitors	Direct thrombin inhibitors
Also known as Coumarins (A poison that inhibits the action of Vit K)	Ends with Xaban	Ends with Gatran
Drugs • Warfarin • Acenocoumarin • Bishydroxycoumarin • Dicumarol	**Drugs** • Apixaban • Rivaroxaban (Longest acting) • Edoxaban • Betrixaban	**Drugs** • Dabigatran • Ximelagatran (banned due to hepatoxicity)
Reduces clotting factors II, VII, IX, X	Inhibits clotting factor X	Inhibits clotting factor II
High risk of bleeding: Warfarin	Low risk of bleeding	Low risk of bleeding
• Requires monitoring o PT (Prothrombin time) with INR	No monitoring is required	No monitoring is required
Antidote: Vit K_1 (Also known as Phytonadione)	• Antidote: Andexanet o Recombinant form of factor Xa	Antidote: Idarucizumab
• Warfarin (DOC) in o Atrial fibrillation + severe mitral stenosis o Mechanical heart valves o Renal failure	Factor Xa inhibitor (Apixaban/Rivaroxaban) and Dabigatran are also known as Novel Oral Anticoagulants (NOAC) • Preferred over warfarin in the following conditions: o In Deep vein thrombosis (DVT)/ Pulmonary embolism (PE) o Transient ischemic attack (TIA) / Stroke o After Knee/Hip surgery	

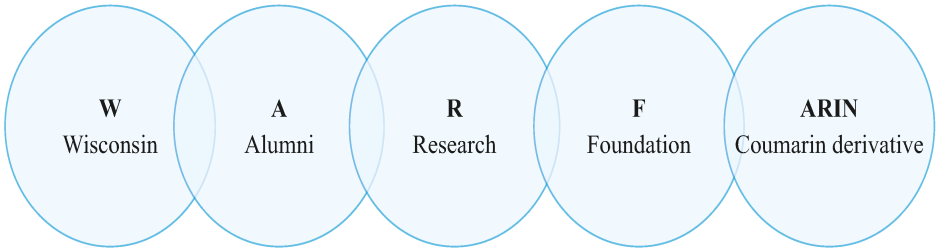
Important Information

- Factor Xa Inhibitors and Dabigatran are contraindicated in Renal failure

Warfarin

00:24:36

Nomenclature



- Initially developed as a rat poison
- Antidote of rat poison: Vit K

Mechanism of action

Synthesis of clotting factors occurs in the liver

↓

In the liver, Vit K (hydroquinone form) is present – the active form

↓

Donates CO_2

↓

Leads to gamma – carboxylation of glutamate proteins

↓

Increased the synthesis of clotting factors II, VII, IX, X

↓

Responsible for synthesis of anti-clotting factors Protein C, S

↓

Gets converted into epoxide (inactive form)

↓

VKOR – C_1 enzyme (Vit K epoxide reductase)

↓

It converts epoxide form into hydroquinone form

↓

Warfarin inhibits VKOR – C_1 in liver

↓

Inhibits the Activation of Vit K

Warfarin
Competitive inhibitor of VKOR-C_1 enzyme in the liver

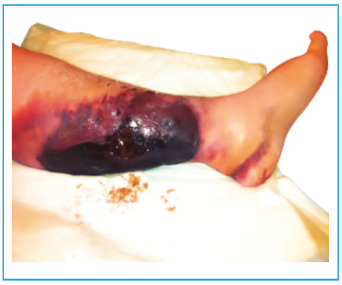
Reduced clotting factor synthesis in liver and
Clotting factors: II, VII, IX, X

Anti-clotting factor synthesis in liver
Anti-clotting factors: Protein C,S

- The 1st factor to be reduced by warfarin Factor VII (within 6 hrs)
- The 2nd factor to be reduced by warfarin is Protein C (within 8 hrs)
- Factor II takes 5 days to be reduced
- The complete anti-coagulant effect of warfarin is after 5 days and hence can't be used in emergencies.

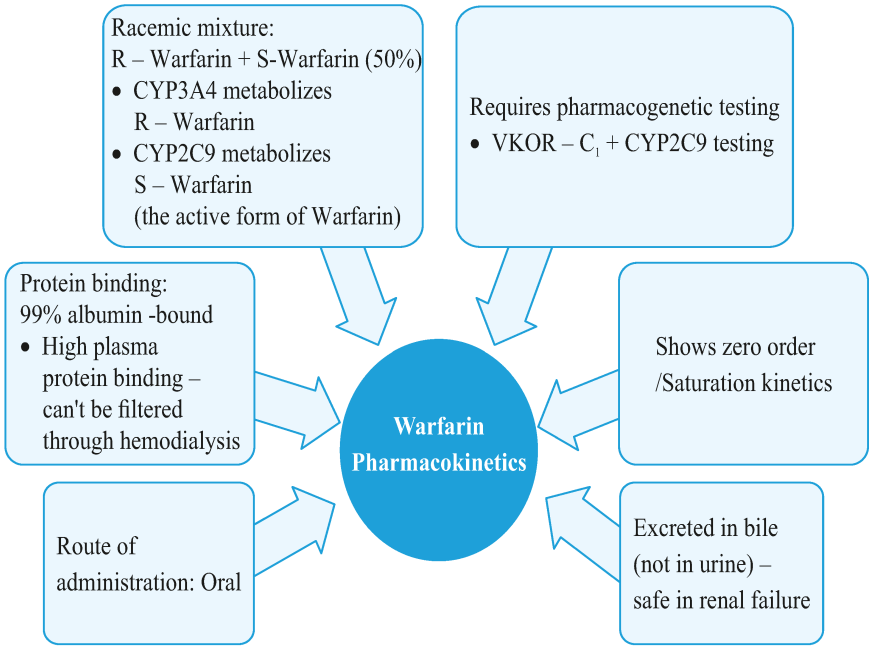
Warfarin as a maintenance anticoagulant drug

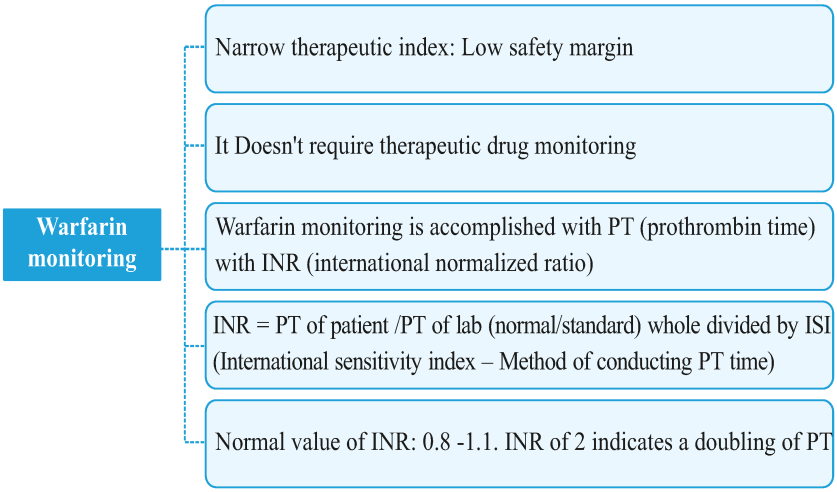
- In the initial 5 days, warfarin increases coagulation due to a deficiency of protein C, S.
  - Manifesting as Dermal vascular necrosis- Limb necrosis, Breast necrosis



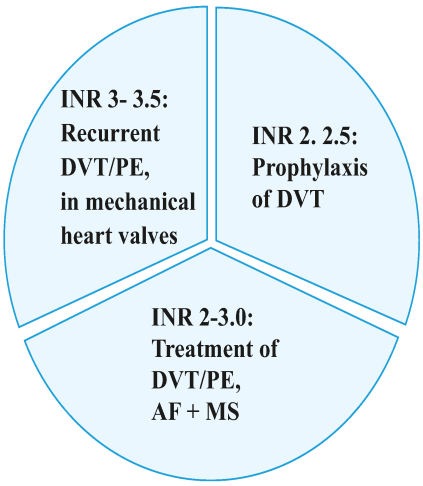
  - Rx: Amputation

- Warfarin requires Heparin injection in the initial 5 days. This is known as Heparin bridge therapy.
- Warfarin is used only as a maintenance anticoagulant drug.





Uses of Warfarin as per INR

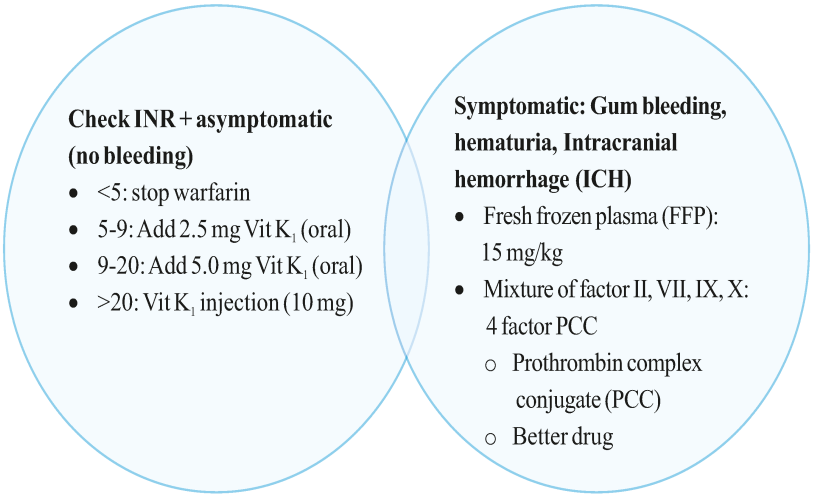


DVT: Deep vein thrombosis
PE: Pulmonary embolism
AF: Atrial fibrillation
MS: Mitral stenosis

Warfarin Drug Interactions

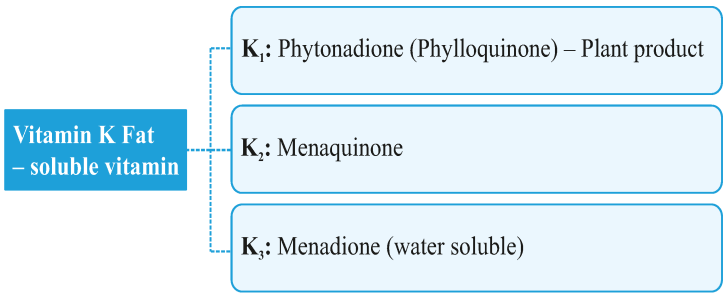
Increase INR: Increases warfarin toxicity	Reduce INR: Reduces the effect of warfarin
• CYP enzyme inhibitor Mnemonic: COKE ○ Cimetidine, Ciprofloxacin ○ Omeprazole ○ Ketoconazole ○ Erythromycin • Aspirin • Antibiotics (causes Vit K deficiency) • Liver disease	• CYP inducers Mnemonic: GPRS ○ Griseofulvin ○ Phenytoin, Phenobarbitone ○ Rifampicin ○ Smoking & Alcohol • Estrogen/OCPs – Increase the synthesis of factor II, VII, IX, X • Renal disease (Albuminuria)

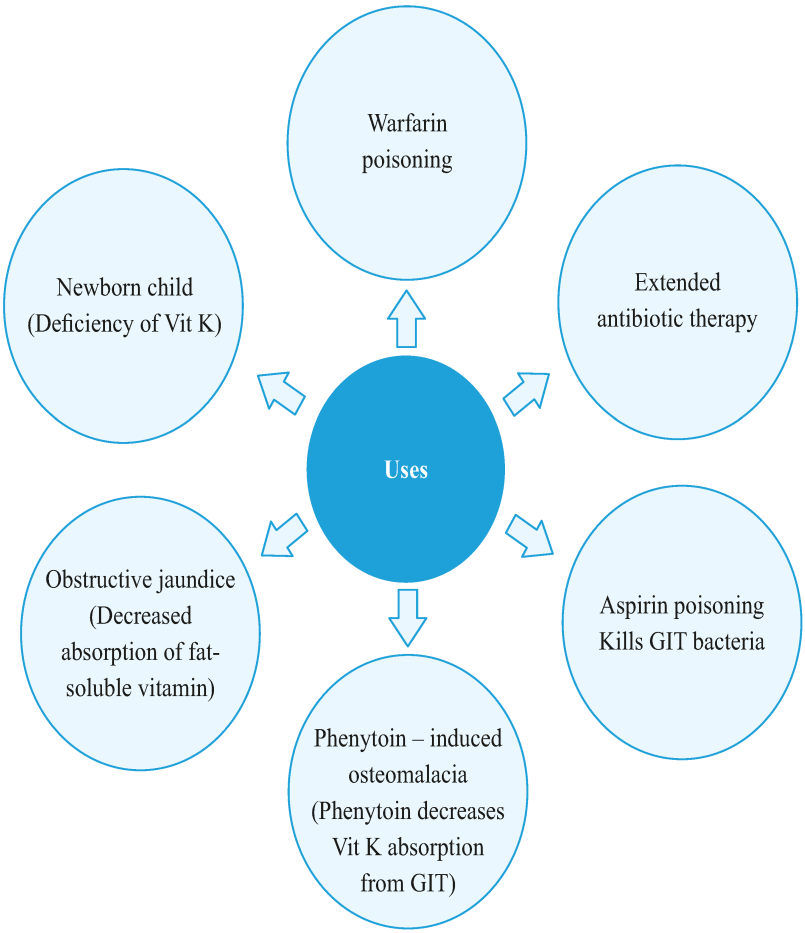
Warfarin Toxicity Management



Vitamin K

00:55:55





Side effects

- Hypersensitivity
- Hemolysis in G6PD-deficient people

27 PARENTERAL ANTICOAGULANTS

- ROA: Subcutaneous or IV injections 00:00:10
  - Not given as IM injections

IM injection
↓
Prevent clotting of blood
↓
Blood is collected inside the muscle
↓
Hematoma formation in muscle

  - IV injection- Requires monitoring (aPTT)

Types 00:01:25

- Divided into two types

Direct thrombin Inhibitors	• ROA- IV

Indirect thrombin Inhibitors	• Other Name- Heparin
	• Three types
	  ○ High molecular weight heparin- IV drug
	  ○ Low molecular weight heparin- Subcutaneous injection
	  ○ Ultra low molecular weight heparin- Subcutaneous injection

Direct Thrombin Inhibitors- Parenteral 00:03:04

- Name of the drugs ends with 'irudin'
- Hirudin
  - Obtained from the saliva of leeches
- Synthetic hirudin derivatives:
  - Desirudin
  - Bivalirudin
  - Lepirudin- Safe in liver disease patients
- Argatroban- Non hirudin
  - Renal safe drug
- ROA: IV
  - Requires aPTT monitoring

Activation of thrombin
↓
Activate the clotting factors of intrinsic pathway
↓
Activation of V, VIII, IX, XI
↓
Production of more thrombin
↓
Continuation of clotting cascade

→ Test for the intrinsic pathway is aPTT

- Only use- Hypersensitivity to heparin
- DOC- Heparin induced thrombocytopenia (HIT)
  - Most preferred - Argatroban > others

Indirect Thrombin Inhibitors: Heparins

00:07:38

MOA

In blood vessel
↓
Heparin binds to antithrombin 3 protein
↓
Change in the structure of antithrombin 3
↓
Conformational changes: inhibits factor X
Structural changes: inhibit factor X and II

Physiology of Heparin

- Chemical nature- Mucopolysaccharide
- Endogenously present in
  - Mast cells/Basophils
  - Epithelial cells of lungs and intestine

In mast cell
↓
Heparin (strongest organinc acid) is attached to histamine (a basic molecule)
Basic Drug →
↓
Basic drug attaches to heparin
↓
Histamine becomes free
↓
Release of histamine from mast cells
↓
Produce anaphylactoid reaction

Important Information

- Anaphylactic reaction: When antigen causes the release of histamine from the mast cells
- Anaphylactoid reaction: When drugs directly release histamine from the mast cells

- Basic that release histamine:
  - Vancomycin- Leads to Red man syndrome
  - Morphine- Causes asthma
  - Tubocurare- Asthma and hypotension

Types of Heparin

- Three types of Heparins
  - High molecular weight (HMW) heparin
  - Low molecular weight (LMW) heparin
  - Ultra Low molecular weight (ULMW) heparin

	HMWH	LMWH	ULMWH
Drugs	Generally termed: Heparins	Ends with 'parin' • Enoxaparin • Dalteparin • Tinzaparin	Ends with 'parinux' • Fondaparinux • Idraparinux
Source	• Ox lung or pork intestine ○ No filtration is required	• Ox lung or pork intestine ○ Filtration is required	• Synthetic ○ Not obtained from animals ○ Pentasaccharide
Other Names	Crude heparin, Unfractionated heparin	Fractionated heparin	Synthetic heparin
MOA	Inhibition of clotting factors X and II (Binds to antithrombin 3)	Inhibition of clotting factors X >>>> II	Inhibition of clotting factor X
Molecular weight	> 15000 kDa	5000 kDa	1500 kDa
Excretion	Reticuloendothelial cells	Urine	Urine
In Renal failure	Safe	Unsafe	Unsafe
$t_{1/2}$	Shortest	-	Longest
ROA	IV	Subcutaneous	Subcutaneous
aPTT monitoring	Required	• Required in case of Renal failure ○ Monitor factor Xa assay	• Required in case of Renal failure ○ Monitor factor Xa assay
Antidote: Protamine sulfate	Very effective (main drug)	Less effective	Not effective
Uses	• Emergency or acute illness ○ Disseminated intravascular coagulation (DIC) → Causes of DIC: – Sepsis – Abruptio placenta – Cancer induced thrombosis – Catheter induced thrombosis	• Prophylaxis of DVT/PE ○ ICU patients ○ Af with MS ○ After knee and hip surgery	

- **Protamine sulfate** 00:24:58
  - Basic drug
  - Antidote of heparin
  - Directly binds to acidic heparin: HMWH >>> LMWH
  - Not effective in ULMW
  - Chemically neutralize the heparin: Chemical antagonist

Adverse Effects of Heparins

- Alopecia
- Hyperkalemia- Inhibit aldosterone synthesis
- Osteoporosis
  - Pregnant females taking heparin injections give calcium supplements to prevent osteoporosis
- Bleeding- Protamine sulfate
- Heparin induced thrombocytopenia
- Reduces blood lipid/ triglyceride levels
  - Because it activates lipoprotein lipases

Heparin Induced Thrombocytopenia (HIT) 00:31:45

- Caused by HMWH >>> LMWH
- Fondaparinux- Do not causes HIT
- Increased risk of thrombosis: Venous > Arterial
  - Venous thrombosis- DVT/PE
  - Arterial thrombosis- MI/Stroke

Pathology Pathology 00:33:46

Attachment of heparin to platelets

↓

Antigenic form (Hapten)

↓

Production of antibodies

↓

Destroy the platelets (Thrombocytopenia)

↓

Causes blockage of blood vessels (Thrombosis)

- Diagnosis- Serotonin assay
  - Platelets when destroyed, release serotonin

Treatment

- Stop Heparins - never start again
- DOC- Direct thrombin Inhibitors
  - Argatroban
  - Lepirudin
- Other drugs include
  - Fondaparinux (ULMWH)
  - Danaparoid (Oral synthetic heparin)
- No role of warfarin

Important Information

Anticoagulants also used as In-vitro anticoagulants

- Hirudin (direct thrombin inhibitor) is used
- Heparin + Anti-thrombin 3 (adjuvant) is used
- Heparin: Not used → It is an indirect thrombin inhibitor
- Warfarin: Not used → Inhibits vitamin K

Anticoagulants in Pregnancy OBG 00:40:25

- DOC- Heparin (LMWH or ULMWH)
  - Do not cross placenta

Warfarin

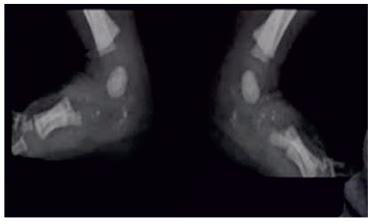
- Contraindicated in first trimester of pregnancy (Up to 12 weeks)
- Teratogenic- Inhibits organ formation

OBG

Warfarin in fetus
↓
Inhibit Vitamin K
↓
↓↓ Osteocalcin
↓
Bone and cartilage defect in fetus
K/s Fetal warfarin syndrome
K/s Chondrodysplasia punctata

- Effected bones include- SLIM (Mnemonic)
  - S- Saddle nose
  - Li- Limb hypoplasia
  - Microcephaly

Saddle nose



Puntate lesions and stippled epiphysis

- Damaged bone in x ray- Stippled epiphysis

Gestational period	Drug of choice
0-12 weeks	• LMW/ULMW Heparin • Contraindication- Warfarin
12-36 weeks	Warfarin > Heparins (LMW/ULMW)
36 weeks to 1 day before delivery	LMW/ULMW Heparin
During delivery	• No anticoagulant drugs are recommended • Increases postpartum hemorrhage
Lactation	Warfarin (preferred), LMW/ULMW Heparin

Antidotes of Anticoagulants

00:46:16

PYQ: FMGE2021

PYQ: NEET 2019

- Warfarin (coumarins) - Vitamin K_1
- Apixaban, Rivaroxaban- Andexate α
- Dabigatran- Idarucizumab
- HMW heparin- Protamine sulfate

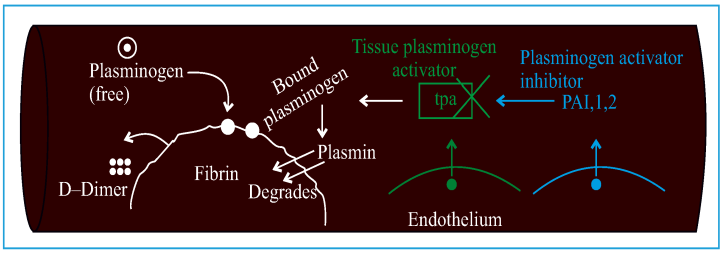
PYQ: NEET PG -INICET 2022

- No antidotes
  1) ULMW heparin
     → Fondaparinux
     → Idraparinux
  2) Direct Thrombin Inhibitor (Parenteral)
     → Hirudin
     → Lepirudin
- Idrabiotaparinux- Contains biotin
  - Antidote- Avidin
- Ciraparantag- Nonspecific antidote for
  - Factor Xa inhibitors- Rivaroxaban, apixaban, edoxaban
  - LMW heparin
  - Dabigatran
  - HMW heparin

28 THROMBOLYTICS AND ANTI THROMBOLYTICS

Fibrinolytics (Thrombolytics)

- **MOA**
  - Activate plasminogen into plasmin
  - Degrades deposited fibrin
- Can lyse a thrombus



In blood
↓
Free plasminogen is present
↓
If excess fibrin is deposited
↓
Plasminogen attaches to the fibrin - Bound plasminogen
↓
Endothelial cells release tpa (tissue plasminogen activator)
↓
Converts bound plasminogen into active plasmin
↓
Fibrin is degraded, and various fibrin degradation products are formed

- D-Dimer: a fibrin degradation product
  - Measuring the amount of d-dimer helps to check the activity of fibrinolysis
- **Excessive activity of tpa**
  - The whole of the fibrin is removed, resulting in bleeding
  - Hence, endothelial cells release PAI 1, 2 (plasminogen activator inhibitor)
    → Inhibits tpa activity

Drugs (all given by IV route) 00:04:16

- **Natural**
  - **Streptokinase**
    → Obtained from group C β hemolytic streptococci
    → $t_{1/2}$: 80 mins
    → Given once in a lifetime as it may produce autoantibodies
  - **Urokinase**
    → Obtained from cultured human kidney cells
    → $t_{1/2}$: 15 mins
    → Can be given in patients with previous streptokinase exposure

- **Recombinant tpa**
  - **A**-Alteplase

→ Human form of tpa
→ Shortest acting drug
→ $t_{1/2}$: 8 mins
→ Inhibited by PAI 1, 2

- **R -** Reteplase
  → Modified form of alteplase
  → $t_{1/2}$: 18 mins
  → Longer acting
  → Resistant to PAI 1, 2
- **T -** Tenecteplase
  → Mutant form of tpa
  → Longer acting
  → $t_{1/2}$: 20 mins
  → Resistant to PAI 1, 2
- Bolus fibrinolytics: Reteplase and tenecteplase
- **Best drug:** Tenecteplase

- All are non specific: Activate both
  - Free plasminogen - Very dangerous
  - Bound plasminogen

- **Tenecteplase**
  - Specific for Bound plasminogen
  - Relatively much safer

Doses

- **Streptokinase**
  - Given as IV
  - 1.5 million IU
  - Continuous infusion over 30 to 60 mins
- **Tenecteplase**
  - 0.5 mg/ kg
  - Dose = half the body weight

Uses 00:12:30

- Only used in emergency
- **Ischemic stroke**
  - Ideal time: within 3 hours
  - Maximum given upto < 4.5 hrs
  - Absolutely contraindicated in hemorrhagic stroke (risk of excessive bleeding)

- **ST elevated MI**
  - Complete blockage by fibrin
  - Ideal time: within 12 hrs
  - Cause opening of coronary artery: Reperfusion therapy
  - Absolutely contraindicated in Non ST elevated MI and unstable angina
    → Mortality may increase
    → Percutaneous coronary intervention can be done

- **Massive pulmonary embolism**
  - If main artery of lungs is blocked
    → No blood enters in to the lung from right heart
    → Leads to RHF and shock
  - **Presents with**
    → Hypotension
    → RVF
    → Right ventricular hypokinesia
  - **Contraindicated in**
    → Mild pulmonary embolism
    → Submissive PE
    → Can be treated with heparin

Side effect: Acute fatal internal bleeding

Antifibrinolytics

00:18:38

PYQ: NEET PG 2021

- **Drugs**
  - Tranexamic acid
  - Epsilon amino caproic acid
- Given to stop active internal bleeding
- DOC for Antidote for fibrinolytics
- **Epsilon amino caproic acid**
  - Most potent drug
  - Antidote for fibrinolytic
- **Tranexamic acid -** Used in
  - Menorrhagia
  - Bleeding esophageal varices
  - Haematuria

29 HEMATINIC, IRON AND CHELATORS

Hematinic

00:00:05

- Hematinic are the agents that increase the formation of blood cells

Drugs that promote RBC growth

Erythropoietin

- Synthesized from kidney
- Available in recombinant form and administered through injection (IV/ SC)
- Ideal drug choice for:
  - Anemia in CKD (Chronic Kidney Disease)
  - Drug-induced anemia: Anti-cancer drugs/chemotherapy and zidovudine

Darbepoetin alpha and epoetin alpha

- Modified forms of erythropoietin
- Longest acting: Darbepoetin alpha PYQ: FMGE 2021
- ROA: IV/SC

Peginesatide

- Erythropoietin attached to a PEG (polyethylene glycol) molecule
- Overall longest-acting drug

Side effects of erythropoietin-like drug

- Hypertension
- Increased viscosity of the blood due increased WBCs - Causes thromboembolism (MI and strokes)

Oral alternatives to erythropoietin-based injection

- Daprodustat
- Roxadustat
- Molidustat
- Inhibits the enzyme hypoxia inducible factor (HIF): Prolyl Hydroxylase

Drugs that promote WBC (leucocytes) formation

00:07:10

Recombinant G-CSF (Granulocyte-Colony Stimulating Factor)

- G-CSF promotes growth of neutrophils
- Filgrastim and PEG-Filgastrim PYQ: FMGE 2021
- ROA: SC
- Approved for the treatment of chemotherapy induced neutropenia
- Filgastrim increases the number of neutrophils - Monocytes are not increased by filgastrim

Recombinant GM-CSF (Granulocyte Monocyte CSF)

- Increases the level of both granulocytes and monocytes
- Sargramostim and molgramostim
- ROA: SC
- Approved for the treatment of chemotherapy induced neutropenia

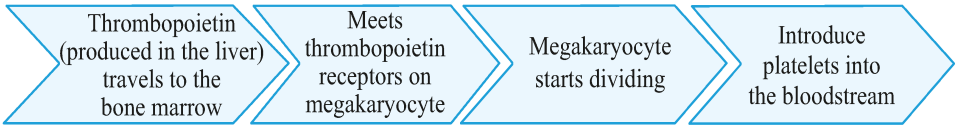
Stem cell transplantation

- G-CSF and GM-CSF are also used for the proliferation of stem cells in bone marrow
- After proliferation: A drug named plerixafor is given to mobilize the stem cell from bone marrow to peripheral blood by blocking the CXCR-4 receptor
- CXCR-4 receptor keeps WBC inside the bone marrow
- Stem cell extraction allows for bone marrow transplantation and stem cell transplantation to treat certain tumors

Drugs that increase platelet count

00:13:00

- Process of platelet production



- IL-11 (interleukin-11) is similar to thrombopoietin

Platelet producing drugs

Romiplostim

- Recombinant thrombopoietin
- ROA: Subcutaneous injection
- Used in the treatment of ITP where autoantibodies destroy bone marrow cells by creating inflammation

Eltrombopag

- Thrombopoietin receptor agonist
- ROA: Oral
- Used in the treatment of ITP and chronic liver disease

Fostamatinib

- Tyrosine kinase inhibitor that reduces inflammation
- ROA: Oral
- New drug for treatment of ITP

Oprelvekin

- Interleukin-11
- ROA: Subcutaneous injection
- Used in the treatment of chemotherapy-induced thrombocytopenia.

Iron

00:18:30

- Most common deficiency
- Iron deficiency leads to microcytic hypochromic anemia

Oral Iron Preparation

Oral iron (60 mg tablets)	Iron content
Ferrous sulfate • Most commonly used preparation and DOC for iron deficiency anemia PYQ: INICET 2022	32%
Ferrous gluconate	12%
Ferrous fumarate • Has the maximum iron content	33%
Ferrous sulfate hydrate	20%

- Ferrous ascorbate
  - New preparation containing Vitamin C (increases iron absorption)
  - Maximum oral absorption/ bioavailability

Factors influencing oral iron absorption from GIT

Factors increasing absorption	Factors decreasing absorption
Acidic environment in the stomach (Vitamin C increases ascorbic acid)	Reduced HCl production →PPI →Antacids
An empty stomach	Tetracycline → Chelates and binds to iron
	Food in the stomach - Tea and coffee (contains phytates and tannates which binds to iron)

Side effects of oral iron

PYQ: INICET 2023

- GIT irritation
  - Nausea/vomiting (most common)
  - Diarrhea or constipation

(Oral iron is always given with food to decrease GIT irritation)

- Blackening of stools and tongue → Indication that patient is taking iron regularly
- If a patient experiences extreme GIT irritation or have poor compliance with oral iron: Indication to start an iron injection (parenteral iron)

Q. Is iron injection more effective than oral preparation?

Ans. No

- Oral iron vs parenteral iron: Equally effective for treating iron deficiency anemia

Important Information

- Earliest response to iron therapy: Increase in reticulocyte count
- An increase in Hb levels in microcytic anemia occurs at around 0.5-1% increase of Hb/ week

Parenteral Iron

Parenteral iron preparations	Route	Anaphylaxis risk
Iron dextran	IV, IM	Yes
Iron sorbitol citrate	IM	Yes
Iron sucrose	IV	No
Ferric gluconate	IV	No

- Allergenic testing is necessary before administering iron dextran/iron sorbitol citrate

- Intramuscular iron can lead to staining of subcutaneous fats
  - When iron is injected into the muscles: Iron can exit the muscle when the needle is withdrawn
  - This can be avoided by giving IM iron injection with the Z technique

Dose calculation of parenteral iron

- Ganzoni formula

Total iron dose = Weight (kg) × [15 - Current Hb (g/dL)] × 2.4 + 500 (to replenish stores)

Important Information

- Hb deficit = 15 - Current Hb (g/dL)

Chelators

00:31:26

- Chelators are the drugs given for the treatment of heavy metal poisoning
- Mechanism of action
  - Chelators directly bind to metals by coordinate bond.
  - This bond makes them non-toxic and is excreted out via urine.

BAL (Dimercaprol)

PYQ: FMGE 2021

- British Anti Lewisite (BAL)
- Used in the treatment of the poisonings
  - Bismuth
  - Arsenic
  - Lead
  - Hg: Mercury
  - Au: Gold
  - Ni: Nickel
  - Sb: Antimony
- BAL is contraindicated in cadmium poisoning and iron poisoning as it forms a toxic complex with these metals.

Calcium Disodium EDTA

00:35:05

- DOC for the poisonings
  - Manganese
  - Lead
  - Cadmium

Important Information

- DOC in lead poisoning is $Ca\,Na_2EDTA$
- BAL and penicillamine are also used in the treatment of lead poisoning

PYQ: FMGE 2021

Penicillamine

00:36:10

- DOC for
  - Copper poisoning
  - Wilson's disease

PYQ: FMGE 2021

- Penicillamine is also used as an immunosuppressive drug for rheumatoid arthritis

Important Information

- Chelators used in Wilson's disease are penicillamine, trientine and tetrathiomolybdate

Deferoxamine

00:37:35

PYQ: FMGE 2021

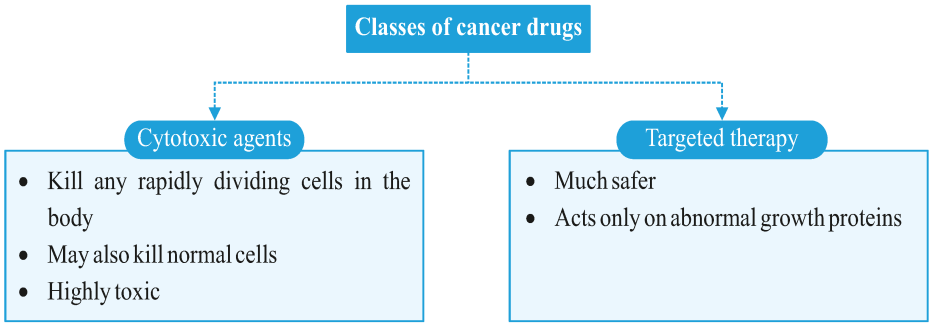
- IV drug
- Orphan drug
- Iron poisoning occurring due to:
  - Thalassemia
  - Hemochromatosis

Deferiprone

- Oral iron chelator
- Iron poisoning occurring due to:
  - Thalassemia
  - Hemochromatosis

30 CYTOTOXIC AGENTS PART-1

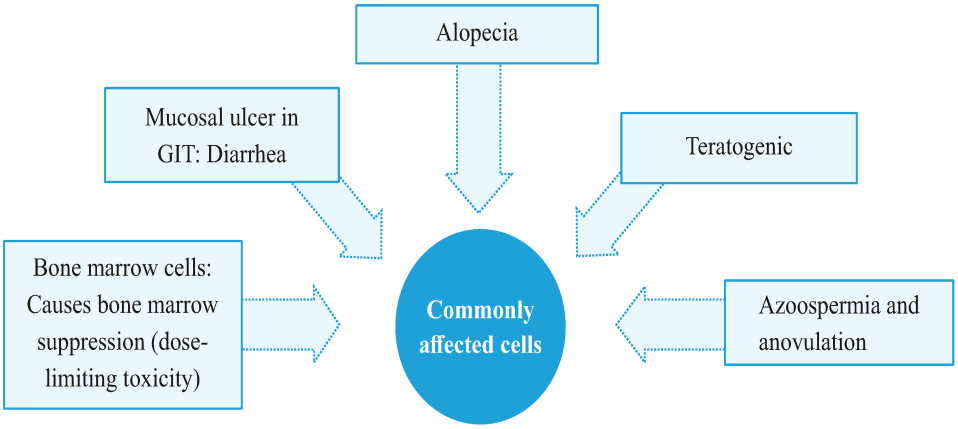
- Cancer is a genetic disease with DNA mutations where abnormal growth proteins are formed leading to uncontrolled cell division.



Cytotoxic Agents

00:02:18

- These drugs are very toxic as they kill any rapidly dividing cells in the body.



- **Note: Mnemonic**- Bharat MATA

Common side effects of Anti-cancer drugs

Bone marrow suppression

00:04:40

Exceptions

- All Cytotoxic drugs produce BM suppression except
  - Vincristine
  - Asparaginase
  - Bleomycin
  - Chlorambucil

Clinical Features

- Anemia
- Leukopenia
- Thrombocytopenia

Management

- **Anemia**: Treated with Erythropoietin injection (SC)
- **Leukopenia**
  - G-CSF (granulocyte colony-stimulating factor)- Filgrastim (SC) PYQ: FMGE 2023
  - GM-CSF (granulocyte monocyte colony-stimulating factor)- Sargramostim, Molgramostim
- **Thrombocytopenia:** Recombinant IL-11 is given (Oprelvekin) PYQ: NEET PG 2023

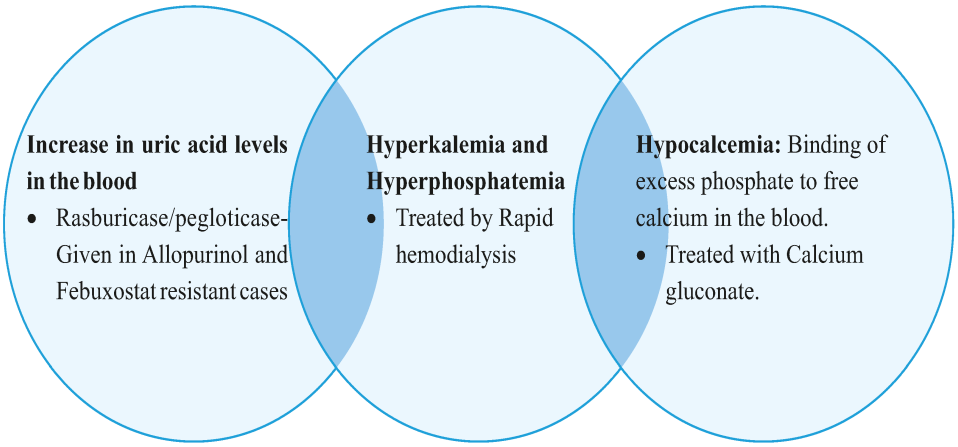
Diarrhea

- Treated with a recombinant form of keratinocyte growth factor
- **Drug:** Palifermin

Miscellaneous side effects of Anti-cancer drugs 00:10:45

Tumor lysis syndrome

- Rapid killing of cancerous cells in the blood is Tumour lysis syndrome.
- **Features and their management**



- **Prevented by**
  - Adequate hydration
  - Allopurinol and Febuxostat inhibit the formation of uric acid

Chemotherapy Induced Nausea and Vomiting 00:14:48

Pathophysiology

Anticancer drugs → Kills GIT cell → Serotonin, NK cells and dopamine are released → Acts at the CTZ area in the brain → Causes Nausea and Vomiting

Most emetogenic

Cisplatin PYQ: FMGE 2023-FMGE 2022

Treatment

- **Early phase: Vomiting upto 24 hours**
  - **Drugs**- Setrons (block 5HT3 receptor)
    → Ondansetron

PYQ: FMGE 2023

→ Granisetron
→ Tropisetron

- **Delayed phase:** If vomiting continues beyond 24 hours
  - Drugs include
    - → Palonosetron
    - → **Pitants:** NK1 antagonists
      - – Aprepitant
      - – Fos-Aprepitant
      - – Rolapitant
      - – Netupitant
    - → **D_2 antagonists:** Olanzapine
    - → Dexamethasone
    - → Cannabinoid agonist
      - – Nabilone
      - – Dronabinol
      - – Increase appetite

Secondary Cancers

Pathophysiology

Anticancer drugs → Inside the cell damages the DNA → Inside the cell DNA repair mechanism is increased → The cell never dies → Induce another type of cancer

Most common secondary cancer

Acute myeloid leukemia

Drugs causing secondary cancer

- **Etoposide:** Causes early cancer (within <3yrs)
- Mitoxantrone
- **Procarbazine**: Maximum risk
- **Cisplatin:** Causes chronic cancer (after >3yrs)

Classification of Cytotoxic Agents

00:22:30

Based on the phase of cell cycle they kill a cell

Cell cycle non-specific
- Kill at any phase of cell cycle
- Alkylating agents
- Platinum compounds
- Cause direct DNA damage

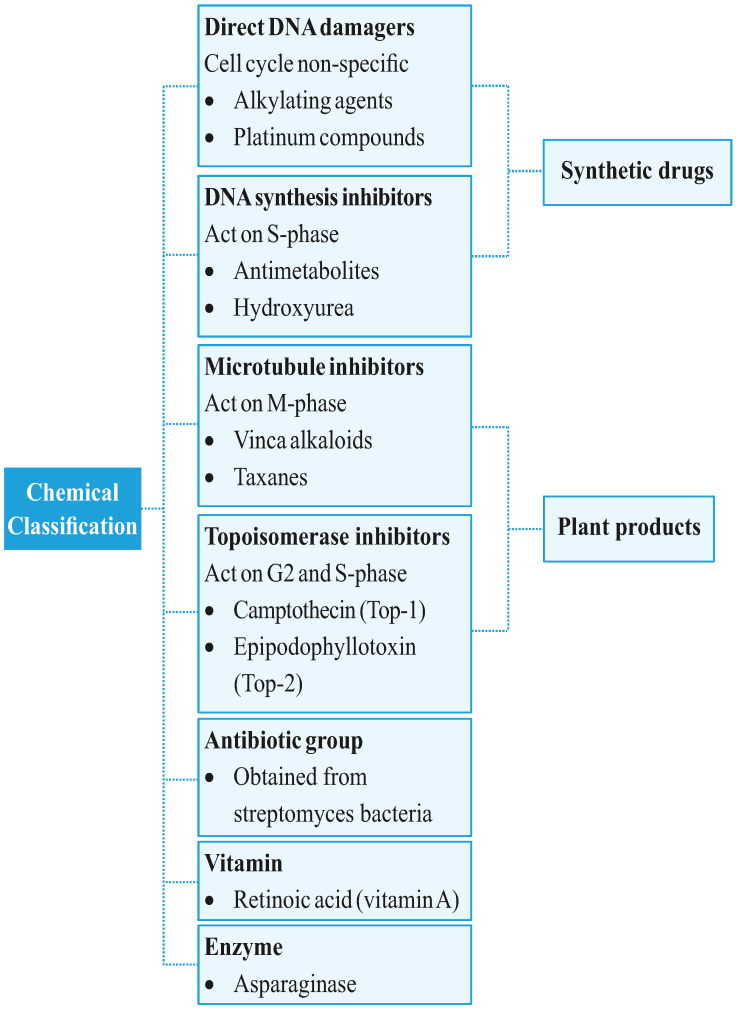
Cell cycle-specific

Drugs acting at G1 phase
- Asparaginase
- Palbociclib: Inhibits CDK4 and 6 (Takes the cell from G1 to S phase)

Drugs acting at S phase
- Hydroxyurea
- Antimetabolites
  - Methotrexate
  - 5 fluorouracil
- Topotecan
- Etoposide

Drugs acting at G2 phase
- Bleomycin
- Etoposide
- Doxorubicin

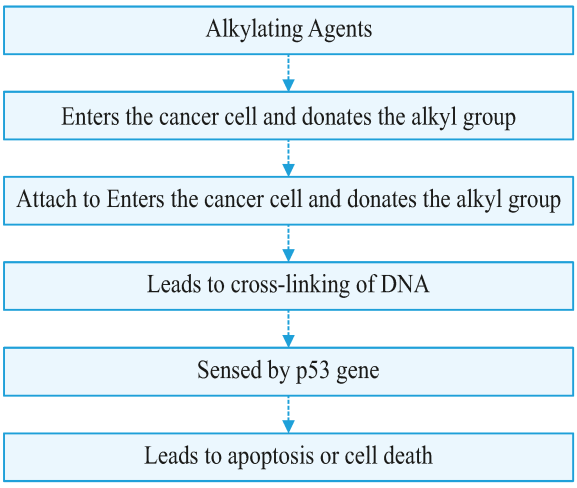
Drugs acting at M phase: Microtubule inhibitors
- Vinca alkaloids
- Taxanes



Alkylating Agents

00:30:25

Mechanism of action



- **Causes of resistance**
  - Upregulation of DNA repair mechanism
  - p53 Gene mutation

- **Drugs**
  - Nitrogen mustards
  - Nitro-ureas
  - Miscellaneous

Nitrogen Mustards

Mechlorethamine

00:34:00

- Also known as Mustin chloride
- 1st Anticancer drug to be made
- Initially used as gasses to kill people during the war by reducing the lymphocyte count and leading to infections.
- Regimens used in the treatment of Hodgkin's lymphoma

Earlier MOPP regimen was given	Now ABVD regimen is used
• Mechlorethamine • Oncovin (Vincristine) • Procarbazine • Prednisolone	• Adriamycin • Bleomycin • Vinblastine • Dacarbazine

- Mechlorethamine was earlier used as a topical cream
  - To treat cutaneous T-cell lymphoma
  - This leads to vesicles or blister formation on the skin
  - Sodium thiosulphate injection was given directly into the blister to treat the side effects

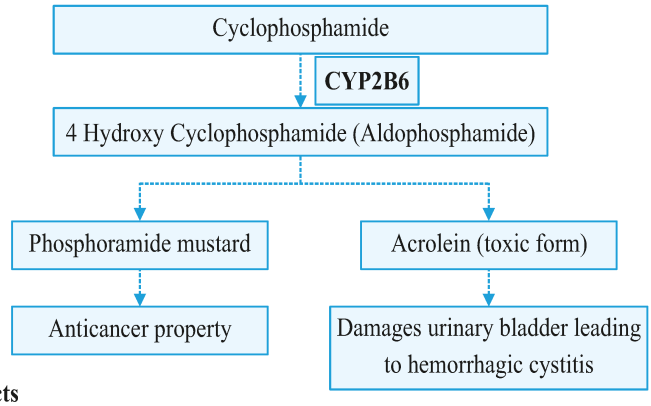
Cyclophosphamide

00:37:50

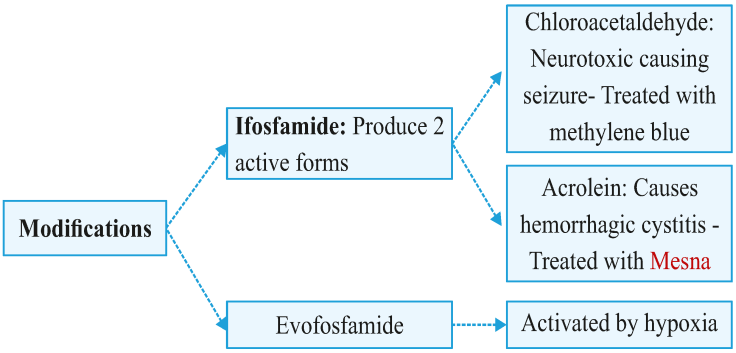
- **Uses**

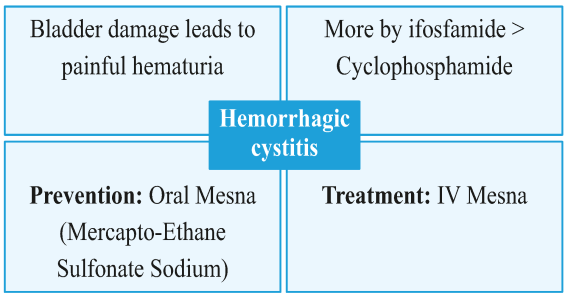
Treatment of cancer	Immunosuppressant (low doses)
• **B**urkitt's lymphoma (DOC) • **B**reast cancer • **O**varian cancer • **N**euroblastoma • Non-Hodgkin's lymphoma	• **W**egner's granulomatosis (DOC) • **A**cute cerebral vasculitis • **R**heumatoid arthritis • **S**teroid dependent nephrotic syndrome

- **Metabolism**



- **Side effects**
  - Ototoxic
  - Hemorrhagic cystitis





Melphalan 00:46:16

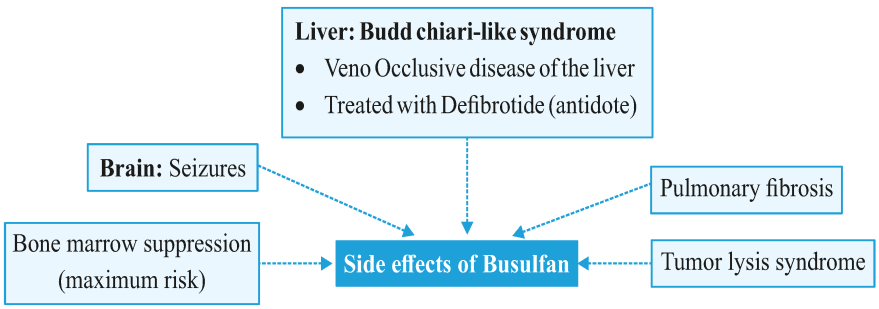
- To treat multiple myeloma (Tumor of plasma B cells)
  - Melphalan + Thalidomide + Dexamethasone
  - Thalidomide alternatives
    - → Lenalidomide
    - → Pomalidomide
  - New drug in place of melphalan: Bortezomib
    - → Proteasome inhibitor
- Also given for myeloablative procedure

Chlorambucil 00:49:00

- Kills mature lymphocytes which are outside the marrow (CLL): 2nd line Treatment
- **1st line Treatment of CLL:** FCR regimen
  - Fludarabine
  - Cyclophosphamide
  - Rituximab
- Least risk of bone marrow suppression

Busulfan 00:51:00

- Kills immature marrow cells and spares mature lymphocytes
- Used for treatment of CML and AML in resistant cases



- Antiepileptics (phenytoin) should be started with busulfan to avoid seizures

Nitrosoureas

00:55:15

- **Drugs**
  - Carmustine (BCNU)
  - Lomustine (CCNU)
  - Semustine (methyl CCNU)
- Also called Bifunctional alkylating agents
- Very effective in entering the brain or have good BBB penetration
- Given in resistant gliomas
- **Side effect:** Prolonged bone marrow suppression (Delayed neutropenia)

Miscellaneous

00:57:25

Temozolomide

- BBB penetration is high
- DOC for Glioma tumors
  - Astrocytoma
  - Glioblastoma multiforme
- **Resistant Cases:** Mustins are given
- Previously used in Melanoma

Dacarbazine

- Used in the treatment of Hodgkin's lymphoma
- Given under the ABVD regimen

Procarbazine

- Treatment of Hodgkin's lymphomas
- Was given under the MOPP regimen
- Side effects
  - Male infertility (Azoospermia)
  - Depression
  - Disulfiram like reaction
    → Procarbazine should be avoided in alcoholics

Thiotepa

Organophosphate used in myeloablative procedure

Altretamine

- Used in the treatment of Ovarian cancer (DOC: cisplatin)
- Given in cisplatin resistant cases

Trabectedin

Used in the treatment of leiomyosarcoma

Lubridectidin

Used in the treatment of lung cancer resistant to cisplatin

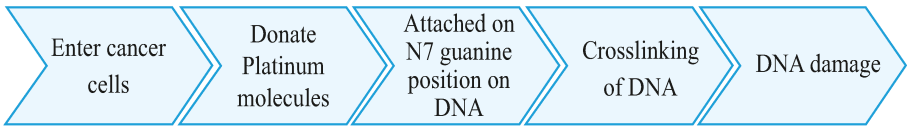
Drugs for Myeloablation	Drugs for stem cell extraction

• Given for bone marrow transplantation
• Drugs
  ○ Busulfan
  ○ Melphalan
  ○ Cyclophosphamide
  ○ Thiotepa
	• G-CSF: Filgrastim
	• GM-CSF: Sargramostim
	• Plerixafor: Blocks CXCR 4 receptor (holds stem cells inside the bone marrow.

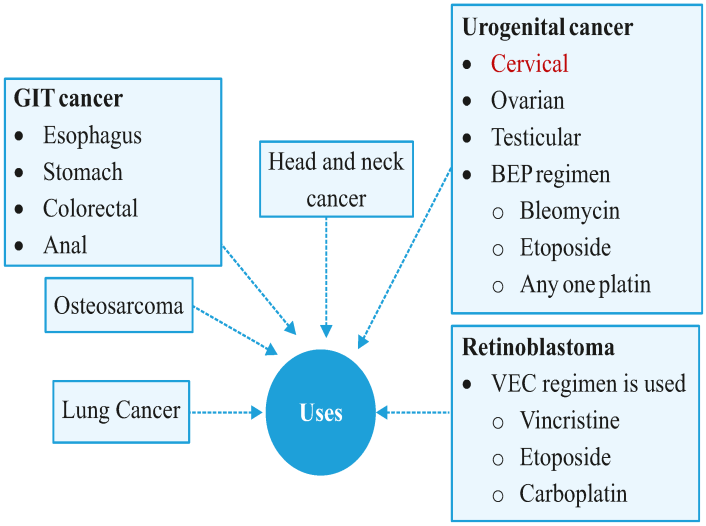
Platinum Compounds

01:05:20

- Cell cycle non-specific drugs producing direct DNA damage
- **Drugs**
  - Cisplatin (Most commonly used)
  - Carboplatin
  - Oxaliplatin
  - Nedaplatin
- **Mechanism of action**



- **Causes of resistance**
  - Upregulation of the repair mechanism
  - Efflux of drug through Cu transporter



- In GIT cancer and head and neck cancer
  - 5 fluorouracil + Platins are given
  - Radiosensitizers
- **Side effects**
  - Vomiting (maximum by cisplatin)
  - Ototoxicity (cisplatin)
  - Nephrotoxicity (cisplatin)
  - Neurotoxicity (oxaliplatin)
- **Least toxicity:** Carboplatin

Plantin-induced nephrotoxicity

01:13:03

- Renal tubules are damaged: Renal tubular acidosis
- Loss of ions in urine
  - Hypokalemia
  - Hypomagnesemia
- **Management**
  - Always give slow IV injection of Platinum
  - Plenty of fluids: To prevent platin accumulation
  - Mannitol + chloride: To remove platin in urine
  - If the kidney is damaged: Amifostine is given (nephroprotector)
- **Amifostine**
  - Given IV only
  - **Nephroprotector:** Protects kidney from platin-induced nephrotoxicity
  - **Radioprotector:** Protects organs from radiotherapy
  - **Not a neuroprotector:** Can't cross BBB

Radiosensitizers	Radio-protectors
• Makes cancer cells prone to radiotherapy • Drugs ○ Cisplatin ○ Hydroxyurea ○ 5 Fluorouracil ○ Gemcitabine	• Protects normal organs from radiotherapy • Drugs ○ Vitamin A, C, E ○ Amifostine ○ N-acetyl cysteine (Liver protector) → Antidote for paracetamol poisoning → Cough suppressants

Drugs Acting on S phase

01:19:45

Hydroxyurea

- Inhibits ribonucleotide reductase
  - Converts ribonucleotide into deoxyribonucleotide required for DNA synthesis
- **Drug of choice: Myeloproliferative disease**
  - Polycythemia
  - Essential thrombocytosis
    → In hydroxyurea-resistant cases, Anagrelide is used
  - Myelofibrosis
- In hydroxyurea-resistant cases of myeloproliferative disorders
  - **Ruxolitinib** is used: JAK kinase inhibitor

Sickle cell disease

- **Cause**
  - Defect in β globin chain

DOC- Hydroxyurea • Increases fetal hemoglobin synthesis as β chain is absent	**Glutamic acid**
Treatment	
Voxelotor • Binds to sickled Hb and prevents sickling • This can be given in a veno-occlusive crisis	**Crizanlizumab**: Inhibits P selectin

31 CYTOTOXIC AGENTS PART-2

Antimetabolites

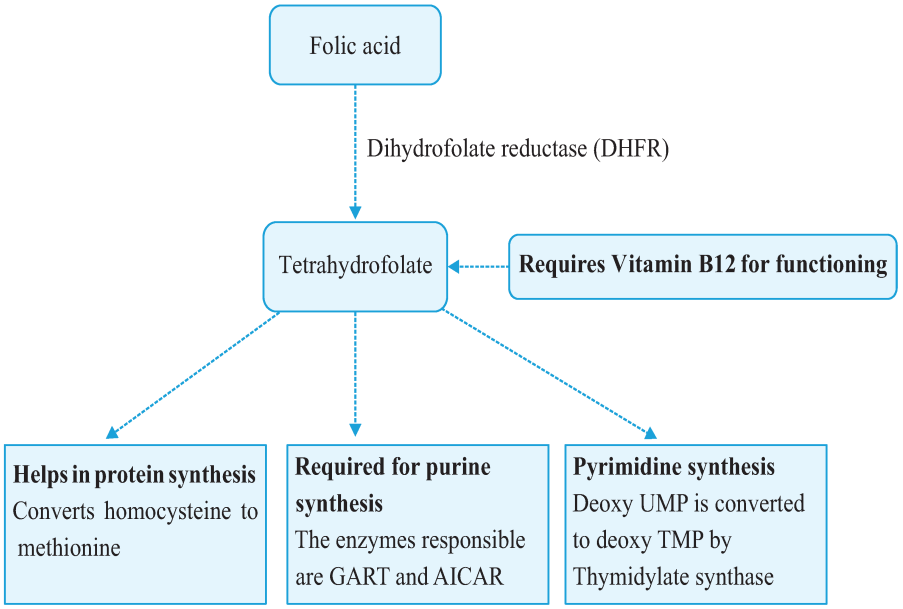
- Structural analogues of DNA components that lead to defective DNA synthesis

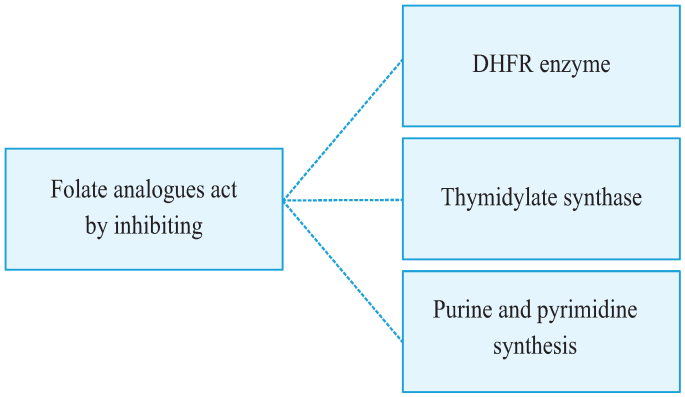
Folate Analogues

00:02:14

- Drugs include
  - Methotrexate
  - Pemetrexed
  - Pralatrexate
  - Lometrexol
  - Raltitrexed
  - Trimetrexate

Mechanism of action





- **Pemetrexed, Pralatrexate and Trimetrexate**
  - Inhibits thymidylate synthase enzyme >> DHFR
  - **Pemetrexed**: DOC for mesothelioma along with cisplatin PYQ: FMGE 2023
  - **Pralatrexate:** DOC in cutaneous T cell lymphoma
  - **Trimetrexate:** Treatment of pneumocystis jirovecii
  - **Antidote for these drugs toxicity:** Folic acid + vitamin B12
- **Methotrexate**
  - Mainly inhibits DHFR >> thymidylate synthase
  - Folic acid can't be converted to THF
  - Drug for methotrexate poisoning: Folinic acid

Methotrexate 00:09:45

Mechanism of action	Methotrexate → Enters into the cancer cells → Glutamate molecules bind to it → Increases in size → Gets trapped in cancer cells → Inhibits DHFR enzyme >> TS, GART, AICAR → Also inhibits Adenosine deaminase → No degradation of Adenosine → Effluxed out of the cell → Kills lymphocytes → Immunosuppression
Causes of resistance	• Decreased formation of polyglutamate • Increased production/ amplification of DHFR gene (main action of resistance) • Efflux of Methotrexate

Uses	**Anticancer drug (high dose 100 mg / day)**
	• Choriocarcinoma (DOC)
	• Osteosarcoma (HD-MTx)
	• Meningeal leukemia (intrathecal methotrexate)
	• Breast cancer
	• Mycosis fungoides
	• ALL tumor
	• Head and neck cancer
	
	Immunosuppressive drug (low dose 30 to 70 mg / week)
	• Organ transplantation
	• Psoriasis
	  ○ Erythrodermic psoriasis
	  ○ Psoriatic arthritis (DOC)
	• Wegner's granulomatosis
	• Sarcoidosis
	• Crohn's disease
	• Rheumatoid arthritis (DOC)
	• Ectopic Pregnancy
	• Abortion
	• Multiple sclerosis (less common)

Side effects	• Megaloblastic anemia (as it is an antifolate drug) • Hepatotoxicity • Pneumonitis
Monitor	• CBC • LFT • Chest X-ray
High dose Mtx	• Rarely nephrotoxic
Highly teratogenic	• Causes Neural tube defects
Management of Methotrexate toxicity	DOC: Folinic acid • Cannot prevent neurotoxicity caused by MTx) → Folinic acid is also known as Leucovorin/Citrovorum factor ↓ **Resistant cases: Glucarpidase** • A bacterial enzyme that degrades MTx ↓ Still resistant **Forced Alkaline diuresis** ↓ **Last resort: Hemodialysis**

Pyrimidine Analogues

00:21:29

- 3 Pyrimidines normally present in the body
  - Cytosine/ cyclidine
  - Uracil/ uridine
  - Thymidine

- Fluorouracil and capecitabine
- Floxuridine
- Cytosine arabinoside
- Azacitidine and decitabine
- Gemcitabine

5 fluorouracil 00:22:25

- Pyrimidine analogues

Mechanism of action	5 fluorouracil → Enters cancer cell → Converted into 5 fluorodeoxyuridine monophosphate → Inhibits thymidylate synthase enzyme → THF increases binding of 5 fluoroauracil with thymidylate synthase • 5 fluorouracil is always combined with THF to increase the effectiveness • MTx is given with THF to reduce the toxicity of Mtx
Pharmacokinetics	• 5 FU is degraded to CO_2 by DHPD enzyme (dihydro pyrimidine) • Contraindicated in DHPD deficiency PYQ: FMGE 2023 ○ Therefore, pharmacogenetic testing is done before giving 5 FU • **Thymidine deficient cell death:** Decreases deoxy TMP production by inhibiting thymidylate synthase enzyme.

Uses	• Given IV for all GIT cancer along with platin
	• Given in breast cancer
	• Topical application on skin: For treatment of
	  ○ Mycosis fungoides (Sezary syndrome)
	  ○ Basal cell carcinoma
	  ○ Actinic keratosis
	• Capecitabine is an oral drug approved for breast cancer treatment

Colorectal cancer	• FOLFOX or FOLFIRI + Bevacizumab
	  ○ Folinic acid
	  ○ 5 fluorouracil
	  ○ Oxaliplatin or irinotecan
	• Bevacizumab
	  ○ Monoclonal antibody
	  ○ Inhibits angiogenesis
	  ○ Inhibits VEGF (vascular endothelial growth factor)

Side effects of 5 FU	• **Mucosal ulcer in GIT:** Leads to fulminant diarrhea
	• **Hand-foot syndrome**
	  ○ Since 5 fluorouracil is eliminated through sweat, it damages the palms and soles when excreted.
	  ○ This condition is also known as Palmoplantar erythrodysesthesia

Hand-foot syndrome

Floxuridine 00:31:30

- New drug for use in colorectal cancer
- Given when cancer has metastasized to the liver
- Directly given in the hepatic artery
- Produce thymidine-deficient cell death

Flucytosine

- Prodrug that inhibits Fungal DNA synthesis
- Useful as a treatment of cryptococcal meningitis
- Produce thymidine-deficient cell death

Important Information

Drugs causing Hand-foot syndrome

- 5 fluorouracil
- Capecitabine (maximum)
- Doxorubicin

PYQ: FMGE2020

Cytosine Arabinoside (Cytarabine) 00:35:15

Uses

- DOC for AML (7C+3 D regimen)
  - Cytarabine for 7 days
  - Doxorubicin for 3 days

ROA

- IV slow injection
- Liposomal preparation: Given intrathecally
  - May damage cerebellum causing Cerebellar toxicity
  - **Features**
    - → Ataxia
    - → Slurred speech
    - → Diplopia
    - → Nystagmus

Azacitidine and Decitabine 00:37:23

- Also called Hypomethylating agents
- MoA: Inhibits methylation of DNA
- Uses: DOC in Myelodysplastic syndrome

Important Information

- Thalidomide is also used in the treatment of Myelodysplastic syndrome.

Gemcitabine 00:39:20

- DOC for Pancreatic cancer
- It is a Radiosensitizer
- **Main side effect:** Pneumonias> ARDS

Purine Analogues 00:40:15

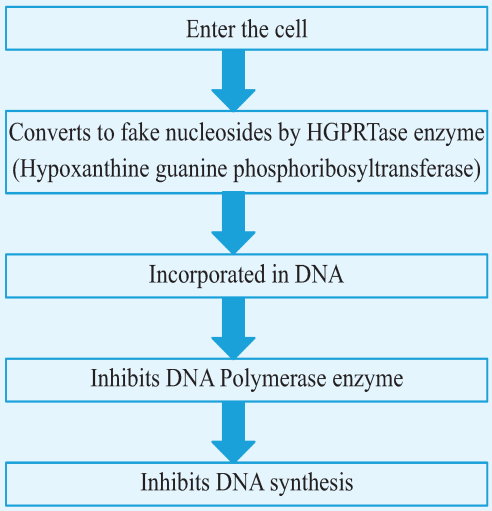
Guanine analogues
- 6 Thioguanine
- 6 Mercaptopurine

Adenine analogues
- Cladribine
- Fludarabine
- Clofarabine
- Nelarabine

6 Thioguanine and 6 Mercaptopurine

- Fake Guanine analogs

Mechanism of action



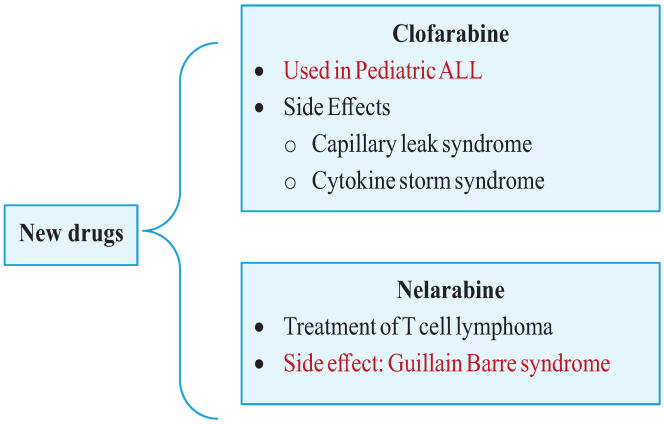
Lesch Nyhan Syndrome	• HGPRTase enzyme deficiency • Both the drugs are not effective in this condition
Uses	• Mainly used in resistant lymphomas • Also used as Immunosuppressive drugs
Azathioprine	• Pro drug • Inside the body, it is converted to 6 mercaptopurine • Azathioprine is not an anticancer drug, it is only used as an Immunosuppressive drug • DOC in IBD and SLE
Side effects	• Main: Bone marrow suppression • Highly hepatotoxic
Monitor	• CBC • ALT levels
Drug interaction of azathioprine and 6 mercaptopurine	• Inside the body, they are degraded by Xanthine oxidase and TPMT (Thiopurine methyltransferase) enzyme • Allopurinol and Febuxostat: Inhibits xanthine oxidase • If given together: Increases the toxicity of azathioprine and 6 mercaptopurine • Management ○ Reduce dose of azathioprine and 6 mercaptopurine by 75% • Check TPMT levels before giving azathioprine and 6 mercaptopurine

Cladribine
- DOC for Hairy cell leukemia and Histiocytosis

Fludarabine
- DOC for CLL under FCR regimen
  - ○ Fludarabine
  - ○ Cyclophosphamide
  - ○ Rituximab

Pentostatin
- Earlier used for
  - ○ CLL
  - ○ Hairy cell leukemia
  - ○ Histiocytosis

- Directly inhibits adenosine deaminase enzyme
- Common side effect: Immunosuppression (opportunistic infections)
  - ○ Can cause pneumocystis jirovecii
  - ○ Hence when these 3 drugs are given cotrimoxazole is always given as a prophylaxis



Plant Products

00:53:25

Microtubule inhibitors	Topoisomerase inhibitors
• Vinca alkaloids • Taxanes • Act on M phase of cell cycle	• Amphotericin • Epipodophyllotoxin • Act on G2 and S phase of cell cycle

A. Microtubule inhibitors

00:54:20

MoA

- These are M phase-specific drugs and are also called spindle poison
- Chromosomes are separated in the M phase by a protein called spindle fibers made up of microtubules
- They also cause cell cycle arrest at metaphase.

Vinca alkaloids	Taxanes
• Inhibit polymerization of microtubules	• Inhibits depolymerization of microtubules
• Inhibits the formation of spindle	• Inhibits movement or over-stabilization of spindle
• Obtained from the Periwinkle plant	• Obtained from Western Yew tree
• Drugs start with -Vin	• Drugs end with - Taxel
Drugs • Vincristine • Vinblastine • Vinorelbine • Vindesine	**Drugs** • Paclitaxel • Docetaxel • Cabazitaxel
Both are highly neurotoxic Toxicity causes Paralytic ileus	
• Produce Foot drop • SIADH	• Glove stock neuropathy
• Most neurotoxic - Vincristine	• Less neurotoxic

Vinca alkaloids

01:01:00

PYQ: AIIMS2020

- **Vincristine**
  - Most neurotoxic
  - Least risk of bone marrow suppression
- **Vinblastine**
  - More side effects of bone marrow suppression
  - Less neurotoxicity
- **Uses**
  - All types of lymphomas
  - Soft tissue tumors
  - Less effective in solid tumors like Osteosarcoma

Taxanes

01:03:20

- Paclitaxel
  - 1st drug to be made
  - As it is insoluble in water, it is mixed in lipid media like castor oil and Methanol and given IV.
  - Eliminated by liver
  - Contraindicated in liver disease
  - It is a short-acting drug and causes a lot of allergic reactions
  - NAB-paclitaxel- Paclitaxel is attached to the surface of albumin making it longer-acting and reducing the risk of allergic reactions
  - Also coated on drug-eluting cardiac stents lead to no growth of cells and not being blocked easily

Important Information

- Drugs coated on drug-eluting cardiac stents
  - Paclitaxel
  - Sirolimus
  - Everolimus

- **Docetaxel**
  - Excreted in urine
  - Contraindicated in Kidney disease
- **Cabazitaxel**
- Used in hormone-resistant cancers
  - Breast cancer
  - Prostate cancer

Other microtubule inhibitors

01:08:10

Drugs	Action	Use
Eribulin	Inhibit polymerization of microtubule	Breast cancer
Ixabepilone	Inhibits depolymerization of microtubule	Breast cancer
Estramustine	Inhibits depolymerization of microtubule	Prostate cancer
Colchicine (spindle poison and causes metaphase arrest)	Inhibits depolymerization of microtubule	Acute gout DOC for karyotyping

B. Topoisomerase inhibitors

01:11:07

MoA

- At the G1 phase, the DNA is highly uncondensed
- **At the S phase** DNA is joined, highly coiled, and an opposite strand is synthesized- Positively coiled.
- **At the G2 phase,** the two strands of DNA remain separated from each other inducing negative supercoiling
- Coiling and uncoiling of DNA is due to Topoisomerase
- Act on G2 and S phase

Drugs

Camptothecin (Inhibit Topoisomerase 1 enzyme)

- **Irinotecan:** Given with 5 fluorouracil (in colorectal cancer)
- **Topotecan:** Given with cisplatin
- Derived from Mayapple plant

Epipodophyllotoxin (inhibit Topoisomerase 2 enzyme)

- **Etoposide**
  - Testicular cancer
  - Hodgkin's lymphomas (under R-EPOCH)
- Teniposide
- Obtained from Happy tree

Irinotecan

- Forms toxic metabolite called SN-38 causing GIT damage
- Main side effect: Diarrhea
- Any drug-induced diarrhea: Treatment is Loperamide

PYQ: FMGE 2023

- Contraindicated in Crigler Najjar syndrome and Gilbert syndrome
  - When glucuronide is attached to irinotecan, it becomes water-soluble and excreted through urine

Antitumor Antibiotics

01:19:00

- **Antibiotics are** chemicals produced by bacteria.
  - Antimicrobial: Given to kill microbe
  - Antitumor Antibiotics: Given to kill cancer cells
- Antitumor antibiotics are obtained from Streptomyces bacteria

Drugs

Anthracycline | Mitoxantrone | Bleomycin | Actinomycin D | Mitomycin | Streptozotocin

PYQ: FMGE2019

Anthracyclines

01:20:30

Drugs

PYQ: FMGE2021

- **These drugs end with – rubicin**
  - Doxorubicin
  - Daunorubicin
  - Idarubicin
  - Valrubicin
  - Epirubicin
- These drugs are Red colored drugs

Mechanism of action

- Topoisomerase 2 inhibitors acting on the G2 and S phase

Use

- All types of cancer (mainly breast cancer): CAT regimen
  - Cyclophosphamide
  - Adriamycin (Doxorubicin)
  - Taxanes

Side effects

- Cardiotoxicity (main SE)
  - Acute myocarditis
  - Dilated cardiomyopathy
    → Bind to iron in myoglobin leading to heart damge
  - Antidote for cardiotoxicity: Dexrazoxane (iron chelator)
  - Maximum toxicity: Doxorubicin
  - Least toxicity: Idarubicin
- Produce red color
- Radiation recall syndrome: Skin damage on sites that were previously exposed to radiotherapy

Mitoxantrone 01:26:12

- Lesser cardiotoxic
- **Given in**
  - Multiple sclerosis
  - AML
  - Prostatic bony metastasis

Bleomycin 01:27:09

Mechanism of action

- Oxidative DNA damage at the G2 phase
- It is peptide antibiotic

Uses

- Hodgkin's lymphoma (ABVD regimen)
- Testicular cancer (BEP regimen)

Advantage

- Bone marrow suppression is not seen

Side effects

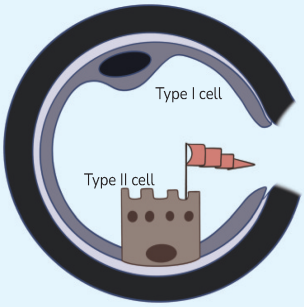
- Bleomycin is inactivated and becomes harmless by hydrolase enzyme and this enzyme is deficient in the lungs (alveoli) and skin

Lungs

Alveoli → Bleomycin kills type 1 cell → No oxygen exchange → Type 2 cells proliferate – Macrophage-like cells → Increase in inflammation → Pulmonary fibrosis

Type 1 cell - Required for gas exchange

Type 2 cell- Makes surfactant



CO levels in the blood are measured by a test known as DL-CO to check if Bleomycin is causing Pulmonary fibrosis or not.

Skin

- Flagellate pigmentation
- Ichthyosis (fish-like skin)
- Raynaud's phenomenon

Flagellate pigmentation

Ichthyosis

Actinomycin D (Dactinomycin) 01:33:35

- It inhibits DNA translation of mRNA and reduces protein production.
- Used for childhood tumors like
  - Rhabdomyosarcoma
  - Wilms tumor
- Also used in choriocarcinoma with methotrexate

Mitomycin 01:34:50

MoA

- Alkylating agent

Uses

- **Urinary bladder cancer**
  - Injection of mitomycin into bladder (Intra-vesical injection)
  - Transitional cell carcinoma
- **Anti-fibrotic action**
  - Inhibits fibrosis and thus preventing strictures / scar formation
  - Given to prevent laryngotracheal stenosis
  - To prevent stricture formation in Anal cancer and Glaucoma surgery

Specific side effect

- HUS – TTP (hemolytic uremic syndrome – thrombotic thrombocytopenic purpura)

Superficial bladder cancer

- **Intra-vesical drugs can be given**
  - Mitomycin
  - BCG vaccine (increases immunity)
- **Contraindicated drugs**
  - Cyclophosphamide
  - Ifosfamide
  - These drugs may cause hemorrhagic cystitis

Other Antitumor antibiotics

01:39:27

Streptozotocin

- Alkylating agent that kills β cells of pancreas
- **DOC for insulinoma**
  - Insulin production should be decreased: DOC is Octreotide > Diazoxide
  - β cells should be killed: Streptozotocin (overall DOC) PYQ: NEET PG 2022

Plicamycin (mithramycin)

- Kills osteoclasts
- Was used for
  - Osteoporosis
  - Paget's disease of bone
- Not used these days
- Now DOC is bisphosphonates

Miscellaneous

01:41:55

Drugs for APML (Acute Promyelocytic leukemia)

- DOC: ATRA (All trans retinoic acid)
- ATRA resistant cases: Arsenic trioxide is given

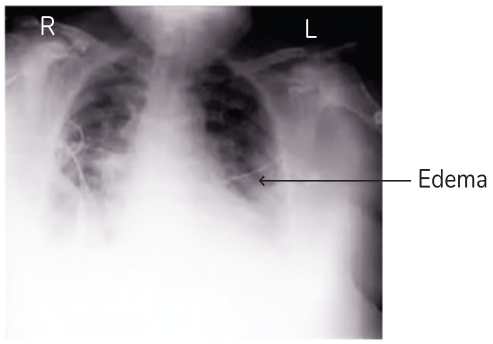
ATRA

Mechanism of action

Acts on retinoic acid receptors → Rapid maturation of cells – Differentiation inducer → Spontaneous apoptosis

Side effects

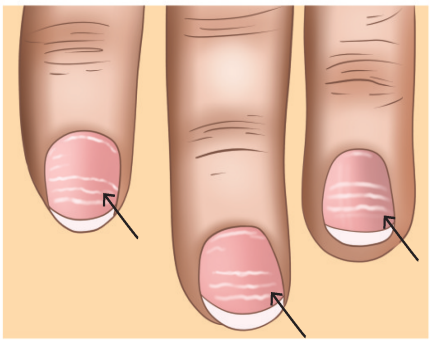
Leukocytic maturation syndrome (retinoic acid syndrome)	Metabolic syndrome
• WBCs in lungs mature causing inflammation in the lungs and leading to lung damage • Causes acute respiratory distress syndrome • Treated with Dexamethasone	• Diabetes • Dyslipidemia • Infertility



Retinoic acid damage

Arsenic trioxide

- Differentiation inducer
- **Side effect**
  - QT prolongation
  - Characteristic Mee's line on nails (white lines)



Mee's lines on nails

L-Asparaginase 01:48:27

Mechanism of action

- An enzyme obtained from E-coli
- Asparagine is an essential amino acid for lymphocyte
- The drug removes asparagine in the blood, preventing division of lymphocyte

Uses

- Treatment of ALL (VPAD – M regimen)
  - Vincristine
  - Paclitaxel
  - Asparaginase
  - Doxorubicin
  - Methotrexate

New drug

- PEG – Asparaginase (Longer acting)

Side effects

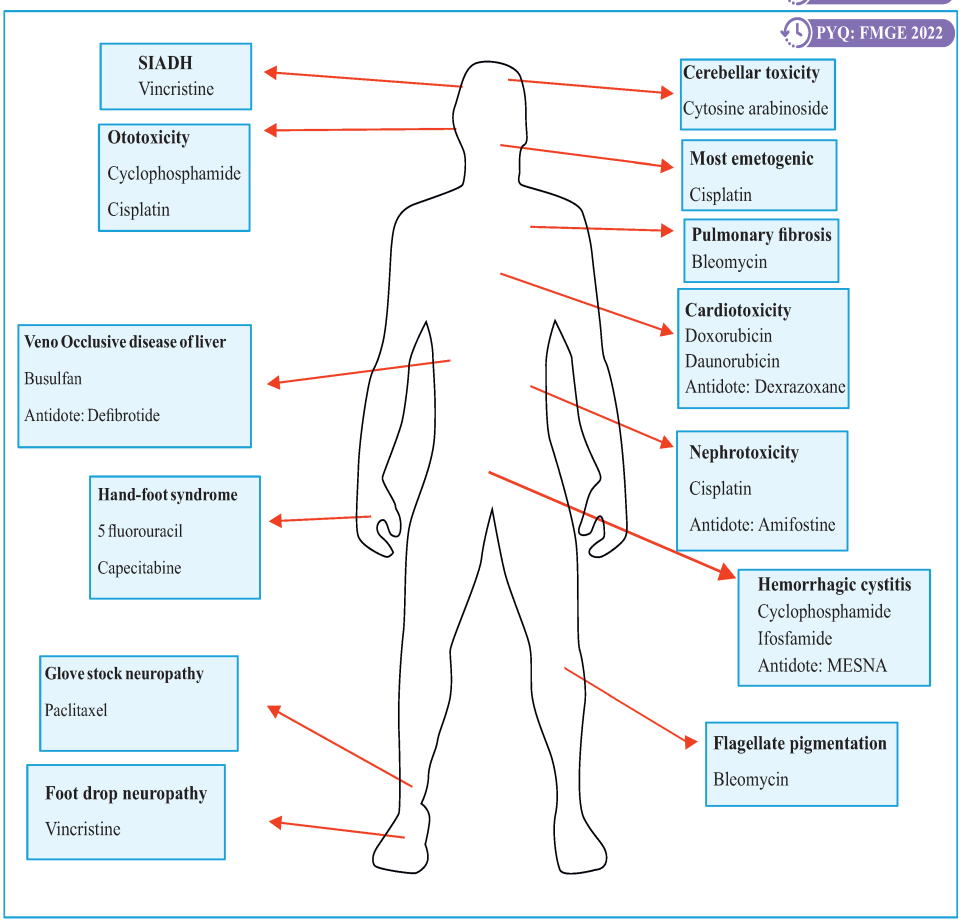
- Reduce albumin levels
- Bleeding
- Damages pancreas

Summary of specific side effects

01:51:35

PYQ: FMGE 2023

PYQ: FMGE 2022



Regimens of choice for various cancers

01:55:48

Hodgkin's lymphoma

ABVD

- Adramycin
- Bleomycin
- Vinblastine
- Dacarbazine

MOPP

- Mechlorethamine
- Oncovin (Vincristine)
- Procarbazine
- Prednisolone

FCR

- Fludarabine
- Cyclophosphamide
- Rituximab

VPAD M

- Vincristine
- Prednisolone
- Asaparginase
- Daunorubicin
- Methotrexate

Histiocytosis, Hairy cell leukemia

CLADRIBINE

AML

- 7C+3D
- Cytarabine + Daunorubicin

Non-Hodgkin's lymphoma

R- CHOP

- Rituximab
- Cyclophosphamide
- Hydroxy Daunorubicin
- Oncovin
- Predinisolone

Colorectal cancer

Folfox / Folfiri + bevacizumab

- Folinic acid
- 5-FU PYQ: FMGE2020
- OXALIPLATIN / IRINOTECAN

Retinoblastoma

VEC

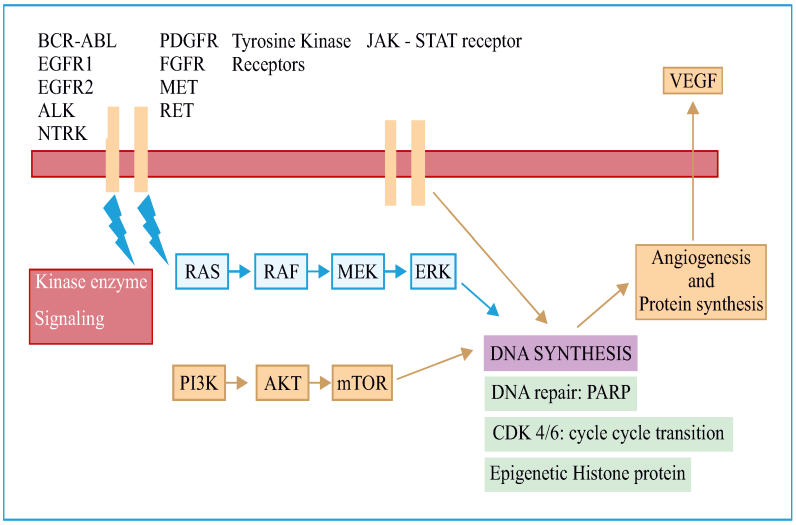
- Vincristine
- Etoposide
- Carboplatin

APML

- ATRA
- Arsenic trioxide

32 TARGETED THERAPY IN CANCERS

- Cancer cell: Express abnormal growth protein leading to uncontrolled cell division



Targeted Therapy in Cancer

00:05:00

Small Molecules	Monoclonal Antibodies

• Molecular weight: <900 Dalton
• Enters inside the cells to inhibit
  ○ Protein kinase receptors
  ○ Signaling molecule
  ○ DNA directly
• Given orally
	• Large molecules (peptides)
	• Act only from the surface
	• These are injectables

Small molecules- Protein Kinase Receptor Inhibitors

00:06:40

- Also known as Tyrosine kinase inhibitors
- These drugs end with -nib
- They are oral drugs
- Metabolised by CYP3A4
- Side effects:
  - GIT: Diarrhea
  - Skin: Rashes

BCR-ABL Tyrosine Kinase Inhibitors

00:08:00

Drugs
• Ponatinib • Imatinib • Nilotinib • Dasatinib • Bosutinib

Uses

- Used in treatment of CML - BCR-ABL tyrosine kinase is mutated in CML
  - DOC for CML is Imatinib
  - In Imatinib resistant cases Dasatinib and Nilotinib is used.
  - Ponatinib is used in Dasatinib and Nilotinib resistant cases.
  - Further resistant cases, Omecetaxine
- Also used in Piladelphia ALL

Side effects

- Imatinib - Diarrhea, skin rashes
- Dasatinib - Pulmonary hypertension and pulmonary edema
- Dasatinib + Nilotinib- QT prolongation
- Ponatinib - Hepatotoxic

Imatinib

- Imatinib binds to ABL kinase of the tyrosine kinase receptor (BCR-ABL) and inhibits attachment of ATP preventing cell division.
- Resistance to imatinib is due to a point mutation in ABL kinase

Platelet-Derived Growth Factor Receptor(c-KIT)

00:13:00

Pathology

- Mutation of Platelet-Derived Growth Factor Receptor leads to GIST (Gastrointestinal stromal tumors)

Drugs approved for GIST

- Sunitinib: Multiple TKI
- Imatinib: Multiple TKI
- Regorafenib
- Ripretinib & Avapritinib: Selective inhibitor of PDGFR
- Imatinib

Bruton's Tyrosine Kinase Inhibitor

00:14:50

Drugs

- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- **Uses (Mnemonic: MaMa Can Sell Water)**
  - **M**antle Cell Lymphoma
  - **M**arginal Cell Lymphoma
  - **C**hronic lymphocytic leukemia
  - **S**mall lymphocytic leukemia
  - **W**aldenstrom macrogamma globulinemia

Non-small Cell Lung Cancer

00:16:00

EGFR (HER1) inhibitors

- Most common mutation seen in non-small cell lung cancer is EGFR (HER1) mutation.
- EGFR: Epidermal growth factor receptor mutation.
- HER1: Human epidermal growth factor receptor - causes lung cancer.
- HER2: Causes Breast cancer.

Generation	Drugs	Explanation
1st Generation	• Erlotinib • Gefitinib	**Erlotinib** • Given in EGFR (+)ve lung cancer, pancreatic cancer • Avoided with food ○ Increased absorption: toxicity **Gefitinib** • Can be given with food
2nd Generation	• Afatinib • Dacomitinib	• Given in resistance of Erlotinib & Gefitinib PYQ: INICET 2023
3rd Generation	• Osimertinib	• Given in resistant cases of Afatinib & Dacomitinib • Given in T790 mutation in EGFR receptor
4th Generation	• Mobocertinib	• Given in resistant cases of Osimertinib
MAB approved	• Cetuximab • Panitumumab • Necitumumab	• Blocks EGFR

Drugs used in EGFR (+)ve lung cancer

- Mnemonic: EGOA
  - Erlotinib
  - Geftinib
  - Osimertinib
  - Afatinib

ALK Inhibitors

00:20:25

Class	Drugs	Description
1st Generation	• Crizotinib	• Crizotinib is used in Anaplastic lymphoma kinase mutation
2nd Generation	• Alectinib • Brigatinib • Ceritinib	• Given in resistant cases of Crizotinib
3rd Generation	• Lorlatinib	• Given in resistant cases of 2nd generation

MET/ HGFR (Hepatocyte growth factor receptor protein) inhibitors

- Capmatinib
- Tepotinib

RET inhibitors

- Selpercartinib
- Pralsetinib

Human Epidermal Growth Factor Receptor-2 (HER2/NEU/ErbB2)

00:22:20

- Mutation causes HER2 (+)ve Breast Cancer
- Drugs used in the treatment
  - Lapatinib: Given in Trastuzumab resistant cases

PYQ: INICET 2023

  - Neratinib
  - Tucatinib

NRTK/TRK Fusions

- Tropomyosin receptor kinase.
- Larotrectinib
- Entrectinib

Multiple Tyrosine Kinase Inhibitors (VEGFR: inhibit Angiogenesis)

00:24:24

Renal Cell Carcinoma	Medullary Carcinoma Thyroid	AML with FLT-3 mutation
• **Mnemonic: Pass Rate Low** • Pazopanib: 1st line RCC • Axitinib • Sorafenib: RCC, HCC • Sunitinib: 1st line RCC, also used in GIST • Regorafenib: RCC, GIST • Lenvatinib: RCC, HCC • Tivozanib: New generation drug for RCC	• Vandetanib • Cabozantinib	• Midostaurin • Gilteritinib

JAK inhibitors

- Ruxolitinib: Jak 1 + 2 inhibitor
- Fedratinib: Jak 2 inhibitor
  - Hydroxyurea-resistant myelofibrosis and Polycythemia

FGFR (Fibroblast growth factor receptor) Inhibitors

- Erdafitinib: Urothelial carcinoma
- Pemigatinib: Cholangiocarcinoma
- Infigratinib: Cholangiocarcinoma
- Side effect: Hyperphosphatemia

Protein Kinase Signalling Inhibitors

00:28:38

- RAS/RAF/MEK/ERK
- PI3K/AKT/mTOR

RAS Inhibitors	B-RAF inhibitors

• NSCLC kRAS Mutant
  ○ Sotorasib
  ○ Adagrasib
	• Most common mutation in Malignant Melanoma is B-RAF mutation
	• Vemurafenib
	• Dabrafenib
	• Encorafenib

MEK inhibitors
- Used in Malignant melanoma
- Trametinib
- Cobimetinib
- Binimetinib
- Selumetinib

PI3K inhibitor
- B Cell Lymphoma (CLL, SLL, FL)
- Idelalisib
- Copanlisib
- Duvelisib
- Umbralisib
- Alpelisib

mTOR inhibitors
- Mammalian target of Rapamycinn
- RCC, Breast cancer, PNET
  - Sirolimus
  - Temsirolimus
  - Everolimus
- Side effects: DM
  - Hyperglycemia
  - Metabolic Syndrome

Other Remaining Targets

00:32:35

	CDK 4, 6 inhibitors	PARP inhibitors (Poly ADP Ribose Phosphate)
Mechanism	• Cell cycle arrest at G1 • Given in Tamoxifen resistant cases	• Inhibits DNA survival PYQ: FMGE2020 PYQ: FMGW2021
Drugs	**Drugs end with -ciclib** • Riociclib • Abemaciclib • Palbociclib	**Drugs end with -parib** • Rucaparib • Iniparib • Olaparib • Talazoparib • S/E: Anemia
Uses	• Estrogen (+)ve Breast cancer	• BRCA (+)ve Breast cancer • BRCA (+)ve Ovarian cancer

Epigenetic Actions

00:35:05

	Histone Deacetylase inhibitors	Histone Methyltransferase Inhibitors
Drugs end with	• -Nostat	• -Metostat
Drugs	• Vorinostat • Belinostat • Panobinostat • Romidepsin	• Tazemetostat
Uses	• Cutaneous T cell Carcinoma • Peripheral T cell Lymphoma • Multiple Myeloma • Cutaneous T cell Carcinoma	• Epithelioid sarcoma

Some New Drugs

00:36:38

Class	Mechanism	Drugs	Use
Proteosome Inhibitor	• Anti Apoptotic enzyme • Increased survival of cell	- Zomib • Bortezomib • Carfilzomib • Ixazomib	• Multiple myeloma • Along with dexamethasone and thalidomide
Nuclear Export Inhibitor	- ZOMIB • Inhibit XPO1	- Inexor • Selinexor	• Multiple Myeloma • DLBCL
Sonic Hedgehog Pathway Inhibitor	• Pathway of embryogenesis	- Degib • Sonidegib • Vismodegib • Glasdegib ○ AML • C/I in pregnancy	• Topical: Basal cell Carcinoma
BCL-2 inhibitors	• Antiapoptotic BCL-2 Inhibitors	- Clax • Venetoclax • Obatoclax	• CLL with 17p deletion
IDH1/2 Inhibitors		- Sedenib • Ivosidenib • Enasidenib	• AML with IDH mutation

Belzutifan

00:40:48

PYQ: FMGE2020

- VHL cancers
- Von Hippel-Lindau Syndrome
  - H: Hemangioblastoma
  - I: Increase risk of RCC
  - P: Pheochromocytoma
  - P: Pancreatic lesions
  - E: Eye dysfunction
  - L: liver, renal, and pancreatic cysts
- Inhibitor of HIF-2α
- Loss of VHL: accumulation of HIF-2α and induction of cell growth and angiogenesis.
- Side effect: Anemia due to the reduction of erythropoietin

CART Therapy

00:42:15

CD-19 CART therapy (Chimeric Antigen Receptor T cell)	LEUCEL	• Axicabtagene Ciloleucel • Tisagenlec Leucel • Brexicabtagene Autoleucel	• Diffuse Large B cell Lymphoma • ALL • ALL, Mantle cell lymphoma

Summary

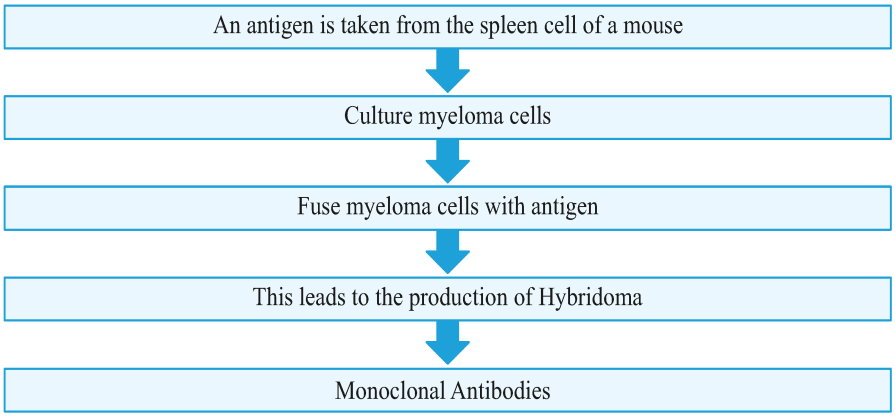
00:43:45

CML	GIST
Bcr-Abl TKI • Ponatinib • Imatinib • Nilotinib • Dasatinib • Bosutinib	• Sunitinib • Imatinib • Regorafenib
HER (+)ve Breast cancer	**Medullary Ca Thyroid**
• Lapatinib • Neratinib	• Vandetanib • Cabozantinib
Non-small cell lung cancer	
EGFR inhibitors • Erlotinib (also in pancreatic cancer) • Gefitinib • Osimertinib • Afatinib	**ALK inhibitors** • Crizotinib • Certinib • Alectinib
Renal cell Ca	**HCC**
VEGRF inhibitors • Pazopanib • Axitinib • Sorafenib • Sunitinib	• Sorafenib • Lenvatinib

33 MONOCLONAL ANTIBODIES

Hybridoma technique

- A technique used to produce monoclonal antibodies



Nomenclature

00:02:20

Suffix: -mab

PYQ: FMGE2019

Drugs ending with	Source	Example
-momab	Mouse- 100%	Tositumomab
-ximab	Chimeric- 50% human + 50% Mouse	Rituximab
-zumab	Humanised- 95%	Transtuzumab
-mumab	Fully human- 100%	Adalimumab

MAB in Tumours

00:04:55

PYQ: FMGE 2021

PYQ: INICET 2022

Trastuzumab	**MoA** • Blocks HER2/Neu receptor **Human Epidermal Growth Factor Receptor** **HER1/ ERB2** • Also known as EGFR • Causes Lung cancer • Treated with Cetuximab **HER2/ ERB1** • Causes Breast Cancer • Treated with Trastuzumab **Side effects** • Cardiotoxic • Should be avoided with Doxorubicin (>30%)
Pertuzumab	• Non-cardiotoxic

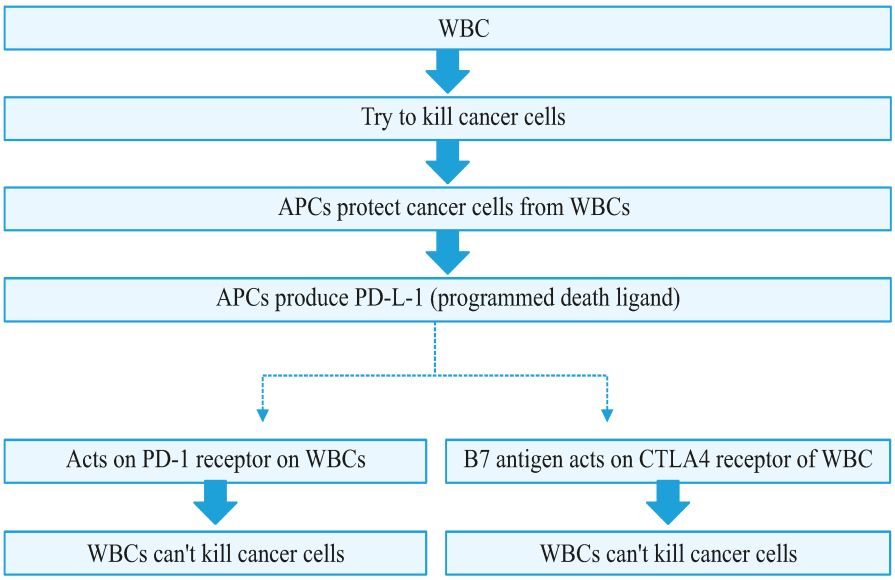
ADO-Trastuzumab	• Trastuzumab is attached to a toxin called emtansine, a DM-1 toxin that cleaves Microtubule • Used in Resistant cases of Trastuzumab for HER2 (+) ve breast cancer
Sacituzumab	• Attached with a toxin called Govetecan • Block Nectin 4A (Microtubule cleaver) • Approved for HER (-) ve breast cancer
Cetuximab	PYQ: INICET 2022 • Blocks EGFR (Erb-2) • Approved for ○ Non-small cell lung cancer ○ Metastatic head & neck cancer ○ Metastatic colorectal cancer
Panitumumab and Necitumumab	**Approved for** • Non-small cell lung cancer • Metastatic head & neck cancer • Metastatic colorectal cancer

Drug	Mechanism	Uses
Rituximab Obinutuzumab Afutuzumab Ofatumumab (Reference)	• Blocks CD20 receptor • CD20 receptor is a marker of B- lymphocyte (kills)	• Re: Rheumatoid Arthritis • L: Lupus erythematosus • I: Idiopathic thrombocytopenic purpura • A: Autoimmune hemolytic anemia • N: Non-hodgkin lymphoma • C: CLL
Tafasitamab	• Blocks CD-19	• B Cell Lymphoma
Olaratumab	• Blocks PDGFR	• Soft tissue sarcoma
Mogamulizumab	• Blocks CCR-4	• Mycosis fungoides (cutaneous T-cell lymphoma) • Also known as Sezary Syndrome
Daratumumab **Isatuximab**	• Blocks CD38	• Multiple Myeloma
Elotuzumab	• Blocks CD319	• Multiple Myeloma
Alemtuzumab	• CD52	• Chronic lymphocytic leukemia (2nd line to fludarabine) • Multiple sclerosis
Dinutuximab **Naxitamab**	• GD2	• Neuroblastoma in children

Immune Checkpoint Inhibitors

00:18:05

Mechanism: cancer bypasses the body's immunity



PYQ: INICET 2023

Blocks CTLA4 receptor	Blocks PD-L-1 receptor	Blocks PD-1 receptor
• Ipilimumab • Tremelimumab	• Atezolizumab • Avelumab • Durvalumab	• Nivolumab • Cepilimumab • Pembrolizumab

- **Note: Mnemonic- New Tumour Drugs Acting At Immune Check Point**

Mnemonic	Drugs	Uses PYQ: INICET 2021
New	Nivolumab	NSCLC, Melanoma, Hodgkin lymphoma
Tumour	Tremelimumab	NSCLC, Melanoma, Hodgkin lymphoma
Drugs	Durvalumab	Endometrial cancer
Acting	Avelumab	Urothelial cancers
At	Atezolizumab	
Immune	Ipilimumab	NSCLC, Melanoma
Check	Cepilimumab	
Point	Pembrolizumab	• Endometrial cancer PYQ: INICET 2022 • > 30 cancers

00:25:00

PYQ: INICWT 2023

Pembrolizumab uses

- **P:** Pulmonary cancer/ NSCLC
  - Tested in Key note trial
- **E:** Endometrial cancer
- **M:** Melanoma
- **B:** Breast cancer
- **R:** Renal cell carcinoma
- **O:** Oesophagus, stomach cancer
- **L:** Lynch Syndrome
  - Mismatch DNA
- **I:** Intestinal cancer
  - Colorectal
- **Z:** Neck & head cancer
- **U:** Urothelial + genital cancer
- **M:** Merkel cell cancer, mediastinal cancer
- **A:** Abnormal microsatellite instability cancer
- **B:** B cell cancer (large)

Bispecific Monoclonal Antibodies

00:29:00

Drug	Target	Uses
Blinatumomab	CD3/ CD19	Philadelphia (-) ve ALL
Amivantamab	EGFR/ MET	NSCLC
Ustekinumab	IL-12/ IL-23	Psoriasis and IBD

Monoclonal Antibody in Psoriasis

00:30:23

Drug	Target	Uses
Ixekizumab **Secukinumab** **Brodalumab**	• IL-17	• Plaque psoriasis
Tildrakizumab **Guselkumab**	• IL-23	• Plaque psoriasis
Ustekinumab	• IL-12 & IL-23	• Plaque psoriasis • IBD (UC/CD)
Efalizumab	• CD11a (LFA) • Leukocyte function antigen	• Plaque psoriasis
Alefacept	• CD2 (LFA)	• Plaque psoriasis

MAB for various diseases

00:32:23

Drug	Target	Approved for
Belimumab	BAFF (B cell Activating Factor)	SLE
Anifrolumab	Interferon-1	SLE
Aducanumab **Lecanemab**	β 1 amyloid	Alzheimer's disease
Emicizumab	Factor 10 + 11	Hemophilia A
Teplizumab	CD-3	T1DM
Eculizumab	C5 complement	• Paroxysmal Nocturnal Hemoglobinuria • HUS-TTP • Devic's syndrome
Ravulizumab **Pegcetacoplan**	C5 complement	Paroxysmal Nocturnal Hemoglobinuria
Palivizumab	Virus	RSV virus
Bezlotoxumab	Toxin B of Clostridium difficile	Pseudomembranous Colitis
Raxibacumab	Directly kills bacteria	Anthrax
Obiltoxaximab	Blocks the toxin produced by bacteria	Anthrax

Angiogenesis Inhibitors

00:37:54

- Inhibition of Neovascularization

Drugs	Target	Use
Bevacizumab	VEGF	Colorectal Cancer
Ramucirumab	VEGFR	Breast cancer
Bevacizumab Ranibizumab Aflibercept Pegaptanib	Inhibits neovascularization in the retina (Intravitreal inj. into the eye)	• Diabetic Retinopathy • ARMD- WET type

- Aptamer: RNA/ DNA sequence- Blocks VEGF

Armed Monoclonal Antibodies

00:42:48

- Also known as Antibody toxin conjugate

Drug	Target	Approved for
Gemtuzumab Ozogamicin	• CD33 + Calicheamicin	• Relapsed AML
Brentuximab Vedontin	• CD30 + Vedontin (microtubule cleaver)	• Hodgkin's lymphoma(refractory) • Large B-cell lymphoma
Belantamab Vedontin	• BCMA + Vedontin (microtubule cleaver)	• Refractory multiple myeloma
Polatuzumab Vedontin	• CD19 + Vedontin (microtubule cleaver)	• Relapsed AML
Moxetumomab Pasudotox	• CD22 + Linked to pseudomonas toxin A	• Hairy cell leukemia

Radiolabeled MAB

Drug	Target	Uses
Y^{90} Irbitumomab I^{131} Tositumomab	CD 20 + Radioisotope	Relapsed Non-Hodgkin's lymphoma

Interleukins in Cancer

00:47:00

- IL-2 increases cell-mediated immunity (recruitment of NK cells, and macrophages) and kills cancer cells

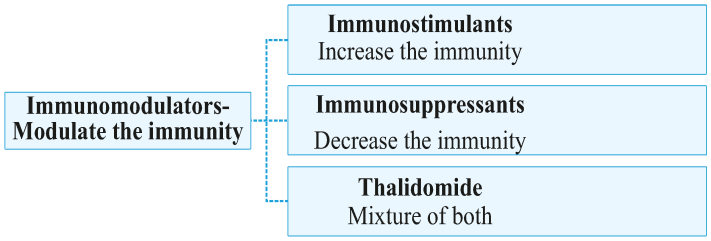
Drug	Target	Uses
Aldesleukin	• IL-2	• RCC • Melanoma
Denileukin Difitox	• IL-2 linked with Diphtheria toxin	• Cutaneous T-cell lymphomas

Cancer Vaccines

00:48:28

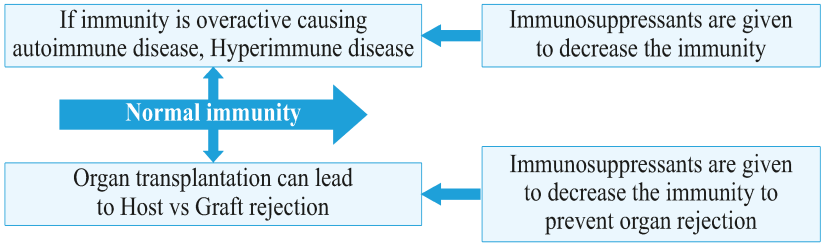
- Cancer vaccines are sensitized T cells directed against the antigens on the surface of the cancer cells.
  - **Sipuleucel T**
    → Directed against Prostatic acid phosphatase Ag
    → Approved in resistant cases of Prostate cancer
  - **Lifileucel:** Used in the treatment of melanoma
  - **T- VEC:** Used in the treatment of melanoma

34 IMMUNOMODULATORS

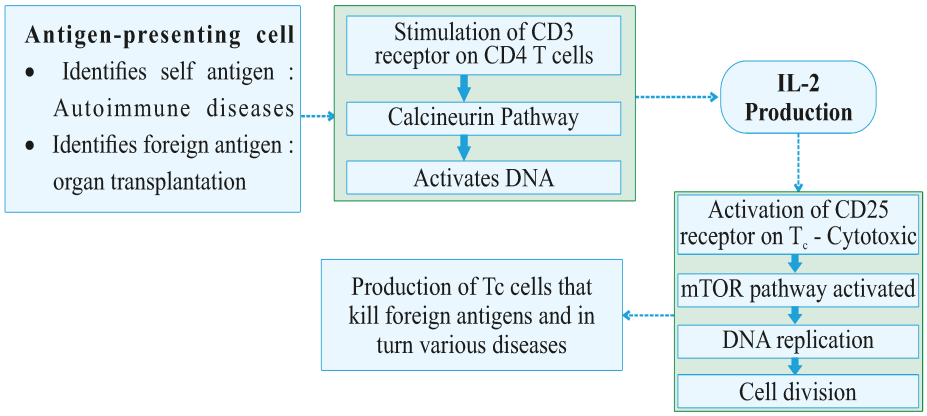


Immunosuppressants

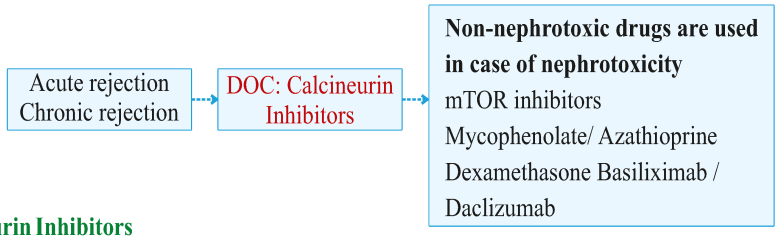
00:00:45



Cell-mediated immunity



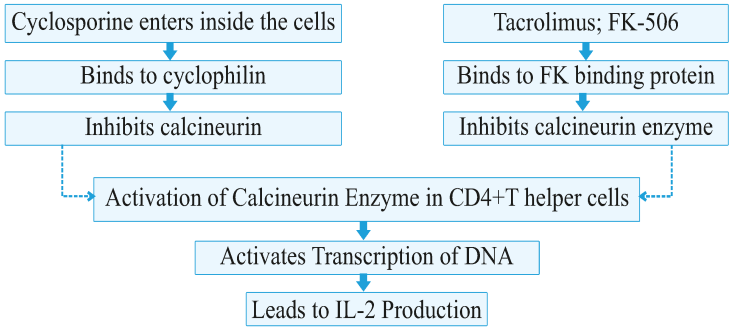
Mechanism	Immunosuppressive Drugs	Description
• Blocks CD3	Muromonab (OKT-3)	• 1st monoclonal antibody • Approved for Organ transplantation
• Calcineurin Inhibitors	Cyclosporine, Tacrolimus	• DOC for organ transplantation
• Block CD-25 (IL-2 receptors)	Basiliximab, Daclizumab	-
• mTOR inhibitors	Sirolimus, Temsirolimus, Everolimus	• Different from Tacrolimus
• Inhibit DNA replication	Mycophenolate, Azathioprine, Anti-cancer	-
• Block all CD receptors	Anti- thymocyte globulin	• Used in Aplastic Anaemia • Organ transplantation
• Most used drug	Corticosteroids	



Calcineurin Inhibitors

Mechanism of action

- Reduce the production of IL-2 from CD4+ T helper cells and reduce cell-mediated immunity



Advantage:

- They don't cause bone marrow suppression

	Cyclosporine	Tacrolimus
Source	• Obtained from soil fungus	• Obtained from bacteria: Streptomyces tsukubaensis
Structure	• Peptide	• Macrolide Antibiotic
Pharmaco-Kinetics	• **ROA:** Given orally, IV, topical • Degraded by CYP3A4 substrate • P-glycoprotein inhibitor and causes Cholestatic Jaundice • Eliminated in bile- Preferred in renal transplant	• **ROA:** Given orally, IV, topical • Degraded by CYP3A4 substrate • No action on P-glycoprotein (MRP-2 protein) • Eliminated in Urine- Preferred in liver transplant
Effectiveness	• Less effective	• > 100 times effective • Can be given in Cyclosporine resistant cases
Specific side effects	• Cosmetic side effect- Hyperplasia of gums (also caused by phenytoin, CCBs, Cyclosporine) • Oral hygiene + Azithromycin(to prevent infection) • Hirsutism	• Alopecia
Common side effects	• Nephrotoxicity ○ Stop the drug ○ Monitor serum potassium level: Hyperkalemia • Hepatotoxicity, hyperglycemia (DM), hyperlipidemia, HTN • Post-transplant Non-Hodgkin's Lymphomas	

Uses	• Organ transplantation
	• Autoimmune disease
	  ○ Atopic Dermatitis
	  ○ Lichen Planus
	  ○ Vitiligo- Topical cyclosporine or Tacrolimus	

New drugs	• Voclosporin- Used in the treatment of Lupus Nephritis	• Pimecrolimus- Used in Atopic Dermatitis

mTOR inhibitors

00:27:25

mTOR

- Mammalian / mechanistic target of Rapamycin

Drugs

- Sirolimus (also known as Rapamycin)
- Temsirolimus
- Everolimus
- Ridaforolimus

Uses:

- In organ transplant
- In resistant cancers
  - Renal cells carcinoma
  - Breast cancer
  - Insulinoma
- Coated on drug – eluting cardiac stents – Prevents restenosis
  - Sirolimus
  - Everolimus
  - Paclitaxel

Side effects

- Insulin resistance leads to Hyperglycemia and Hyperlipidemia
- QT prolongation

Advantage

- Non – nephrotoxic

Mycophenolate Mofetil

00:32:02

Pharmacokinetics

- A prodrug converted into Mycophenolate (active)

Mechanism of action

Inhibits IMPD (Inosine Monophosphate Dehydrogenase enzyme) → **Inhibit Denovo Guanine production** → **Inhibits cell division**

Uses

- Organ transplantation
- SLE

Side effects

- Bone marrow suppression, GIT ulcers, diarrhoea

Immunostimulants

00:34:25

- **Note: Mnemonic- LIBIA**

Levamisole

- Anti – helminthic used in the treatment of Ascariasis
- Immunostimulant
  - Stimulates lymphocyte
  - Treats steroid refractory nephrotic syndrome
- Side effects: In high doses, becomes immunosuppressant causing Aplastic Anaemia
- Immunostimulant drugs – Contraindicated in pregnancy

Imiquimod

- Stimulates Toll- like receptor – TLR -7 on macrophages, NK cells (increase immunity by increasing IL- 1 , IL-2 , TNF α)
- Used topically in
  - Basal cell carcinoma
  - Actinic keratoses
  - Genital warts
    - → Due to HPV / Condyloma
    - → Cryotherapy is used as treatment during pregnancy
- Contraindicated in Pregnancy

BCG Vaccine

- Live vaccine
- Intra vesical injury – Given directly into the urinary bladder
  - Treats superficial bladder cancer
  - A similar drug is Mitomycin

IV-Ig

- Intravenous immunoglobulin is a mixture of all antibodies from pooled human plasma
- Neutralises autoantibodies in autoimmune disease
  - Guillain Barre Syndrome
  - Kawasaki disease
  - Multiple Sclerosis
  - Myasthenia gravis
- Contains IgG (90%)

Aldesleukin

- Recombinant form of IL-2
- Treats renal cell carcinoma, Melanoma
- Causes excessive inflammation leading to Cytokine storm and Capillary leak syndrome

Thalidomide

00:44:00

Mechanism of action

Anti – tumor	Immunomodulatory
• Inhibits NF-KB • IL-6 • BCL-2 • Angiogenesis	• Reduce the production of TNF-α • Increase the production of IL-2 and IFNγ

Uses

- Type 2 lepra reaction – Erythema Nodosum leprosum
- Orogenital ulcers- Bechet's disease, HIV (+)ve
- Multiple myeloma
- Myelodysplastic syndrome

Enantiomeric conversion

- Thalidomide has 2 Enantiomers
  - **R- form**
    → Sedative drug
    → Effective in morning sickness: Vomiting in 1st Trimester
  - **S- form**
    → Highly teratogenic: Phocomelia
- The conversion of R- form to S- form and vice versa is called Enantiomeric conversion
- Due to this property, it is contraindicated in pregnancy (Category X drug)

Thalidomide in pregnancy

- Thalidomide in fetus causes teratogenic abnormalities known as Phocomelia / Amelia (Small limbs / no limbs)
- This is caused due to the inhibition of Cereblon protein in the fetus

Side effects

- Sedation, Constipation, Neurotoxicity (dangerous)
  - Peripheral sensory neuropathy
  - Carpal tunnel syndrome

  } indications to stop Thalidomide
- Thromboembolism – DVT/ MI/ Stroke

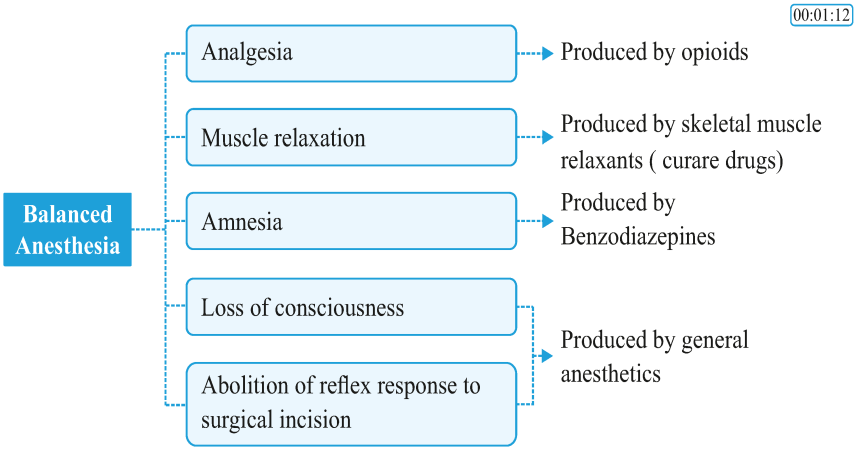
Thalidomide congeners

- Lenalidomide
- Pomalidomide (Most effective)
- Used in Multiple myeloma, Myelodysplsatic syndrome

35 GENERAL ANESTHETICS

- **Anesthesia-** Reversible loss of sensation to a painful/surgical incision
- **General anesthesia-** Acts on CNS , produces loss of consciousness
- **Local anesthesia-** Acts outside of the brain , no loss of consciousness

00:01:12



- No single drug can produce balanced anesthesia, hence a combination of drugs is used to produce balanced Anesthesia

History of Anesthesia

00:04:17

- Father of Anesthesia: Morton
  - Demonstrated the use of Ether as a general anesthetic (rarely used)
- Father of Modern anesthesia: Long
- Term balanced anesthesia: Lundy & Waters

Stages of Anesthesia

Anaesthesia

00:05:29

- Gudel defined stages of anesthesia by using Ether as an anesthetic agent.
- Modern general anesthetics are fast-acting and the stages are not seen clearly.

Stage of Analgesia
- Loss of pain, but the patient is conscious
- Autonomic responses like BP, HR and RR are normal
- Used during Labour

Stage of Delirium & excitement
- Ether suppresses inhibitory neurons and increases excitatory senses
- The patient has excessive movements, struggles, irregular breathing, cough, increased muscle tone, increased BP, HR and RR
- This is an undesirable stage: No use

Stage of surgical anesthesia
- Desirable stage for surgery
- Loss of reflexes
- Stable blood pressure, heart rate, respiratory rate
- Divided into 4 planes

Stage of medullary paralysis

- The medulla has a respiratory center
- Respiratory depression occurs and may lead to coma/death
- This is an undesirable stage

Classification of General anesthetics

00:13:19

Inhalational GA		Intravenous GA
Inhalational gases	**Volatile liquids** (Vapors are produced by heating)	
Mnemonic: NEX • Nitrous oxide • Entonox • Xenon	**Mnemonic: CETCH MyVSIDE** • Chloroform • Ether • Trilene • Cyclopropane • Halothane PYQ: FMGE2019 Fluranes (Gases) • Methoxyflurane • Sevoflurane • Isoflurane • Desflurane • Enflurane	**Mnemonic: TEMP Kelvin** • Thiopentone • Etomidate • Methohexitone • Propofol • Ketamine

Mechanism of action of GA (Suppress CNS neurons in the brain)

00:17:34

- **Increase inhibitory neurons/impulses**
- **Increase the action of GABA-** Act on GABA-A chloride channel, open
- **Increase glycine chloride channel opening-** Chloride ions inside neurons cause Hyperpolarization of neurons
- **Open potassium channels:** TREK channel (Two Pore Potassium channel)

- **Reduce excitatory neurons/impulses**
- **Block Glutamate receptors (NMDA antagonist)-** Glutamate is an excitatory neurotransmitter
- Main MOA of Ketamine, Nitrous oxide, and Xenon

- All GAs have this overlapping action

Inhalational agents

- Gases stored in a cylinder
- **Precautions:**
  - Color coding of cylinder
  - Pin index safety system

Safety precautions with Inhalational agents

00:22:46

	Color coding of cylinders	Pin index safety system (Numerical on the tube)
Air	Grey body + black/white shoulder	1,5
Oxygen	Black body + white shoulder	2,5
Nitrous oxide	Blue	3,5
Entonox (Nitrous oxide + Oxygen)	Blue body + white shoulder	7
Carbon dioxide (>7.5%)	Grey	1,6
Carbon dioxide (<7.5%)	Grey	2,6
Cyclopropane	Orange	3,6

Volatile liquids in vaporizers

00:24:51

- Vaporizers are heated to form gases

Volatile liquids	Color of vaporizers
Halothane	Red
Sevoflurane	Yellow
Isoflurane	Purple
Desflurane	Blue
Enflurane	Orange

Properties of inhalational GA

Anaesthesia

00:25:54

Duration and dose of a GA depends on

Minimum Alveolar Concentration (MAC)
- The potency of GA is inversely proportional to the dose of GA

Blood Gas Partition coefficient
- Speed of action of GA
- Fast/slow acting

Minimum Alveolar Concentration (MAC)

- The concentration of GA, in the alveoli of the lung that produces unresponsiveness to the surgical incision in 50% of patients
- In 100% of a GA: A, if 25% of alveoli is occupied by A, which enters blood and brain
  - 50% of the patients do not respond to surgical incision.
  - MAC: 25% (0.25)
- In 100% of a GA: B, if 75% of alveoli is occupied by B, which enters blood and brain
  - 50% of patients do not respond to surgical incision.
  - MAC: 75% (0.75)
- Potency of A> Potency of B
- MAC provides the dose of GA
- MAC is inversely proportional to potency
- MAC is directly proportional dose

Blood gas partition coefficient

- In the blood, the GA either remains in dissolved form (Soluble form) or can be in a gaseous form (Bubbles, Undissolved/insoluble form)
- Blood (dissolved)/ Gas (undissolved) partition (different states)
- Gaseous form enters into the brain to produce unconsciousness
- Blood/dissolved form doesn't enter into the blood
- The B/G coefficient is indirectly proportional to the speed of action
  - High B/G: Slow induction and the drug is more soluble
  - Low B/G: Fast induction and the drug is less soluble
- B/G partition coefficient gives the speed of onset & recovery from the anesthetic effect

Mnemonic	Drugs	MAC value (Potency)	B/G partition coefficient value (Speed of onset & recovery)
My	Methoxyflurane	0.16% (most potent GA)	Xenon (Fastest-acting GA)- 0.14
T	Trilene	0.2	Desflurane (Fastest-acting Flurane)
H	Halothane	0.7	Nitrous oxide
I	Isoflurane	1.15	Sevoflurane
E	Enflurane	1.95	Enflurane
S	Sevoflurane	2.05	Isoflurane
Does	Desflurane	6 (least potent flurane)	Halothane
Cross	Xenon	33	Trilene
Not	Nitrous oxide	104 (least potent)	Methoxyflurane (Slowest-acting Flurane)
			Ether (slowest acting GA)- 12

Why Nitrous oxide cannot produce anesthesia in all patients?

- MAC value: 104%
- Nitrous oxide has to occupy >100% of the volume of alveoli to produce unresponsiveness in 50% of the patients to surgical incisions, which is not possible
- Least potent, requires a high dose
- Not a complete anesthetic

1. **Nitrous oxide** 00:44:33

MOA	• Also known as Laughing gas as it produces a euphoric effect (happiness) by stimulating opioid receptors • It is also an NMDA receptor antagonist
Properties	• Overall, least potent GA • MAC: 104% (highest)- Cannot produce GA • B/G: Low- Fast onset and Fast Recovery

3 properties of Nitrous oxide	Concentration effect	Second gas effect	Diffusion hypoxia
	• Due to the low B/G partition coefficient, nitrous oxide diffuses rapidly from the cylinder to the brain through the alveoli • This creates negative pressure in the alveoli due to which it withdraws more nitrous oxide from the cylinder (automatically)	• Due to negative pressure, additional gasses are also withdrawn into the alveoli • Nitrous oxide is used as a carrier gas • Commonly used gases are Oxygen and Halothane	• Diffusion hypoxia – On completion of surgery, sudden stopage of N_2O leads to its diffusion back into the alveoli leading to hypoxia as no oxygen is present in the alveoli • Treatment: 100% oxygen for 5 mins
Uses	• Used as a carrier for other gasses. • Acts on Opioid receptors to produce an analgesic effect- Used in dental procedure		
Side effects	• Contraindicated as it is highly diffusible into body cavities leading to their expansion. ○ Pneumothorax ○ Pneumoperitoneum (during laparoscopy) ○ Ocular surgery ○ Middle ear surgery • Nitrous oxide reacts with Cobalt (Vitamin B12) causing the inactivation of Vitamin B12 (nerve growth) ○ Vitamin B12 deficiency: → Megaloblastic anemia → Peripheral neuropathy → Subacute degeneration of the spinal cord ○ Vit B12 converts Homocysteine (toxic) into Methionine → Contraindicated in Homocysteinemia		

2. **Entonox** 00:56:56
   - A mixture of Nitrous oxide (50%) and Oxygen (50%)
   - These two gases lose their individual property after mixing and behave as a single gas. This is called the Poynting effect.
   - Stored and transported in a single-cylinder.
   - Commonly seen in Ambulance

3. **Xenon** 00:58:42
   - Xenon has high MAC value and a low B/G partition coefficient like Nitrous oxide
   - Used as a carrier for a second gas
   - Safest GA in Hepatic/Renal diseases as it is an inert gas
   - It is an NMDA receptor antagonist
   - It is a rare gas obtained from the environment , production is costly
   - **Side effects:** It is heavier than air, so if given by inhalation can lead to difficulty in breathing

4. **Chloroform** 01:01:21
   - Old GA now not in use.
   - Highly hepatotoxic (hepatic cancer) and cardiotoxic.

5. **Ether**
   - Old and safest GA, especially if the anesthetist is inexperienced and it was commonly used on the battlefield.
   - Maximum B/G partition coefficient: 12
     - Slowest acting drug
     - Less risk of respiratory depression
   - Good analgesic action, muscle relaxant property
   - **Side effects**
     - Provokes asthma/bronchoconstriction as it is an irritant and has a pungent smell
     - **As it is Inflammable**
       → Never given during electrocautery
       → Not used in open circuits (exhalation of ether into open air causes explosion)

6. **Trilene**
   - The most potent analgesic action among all Gas
   - Given during labor
   - Not used in the closed circuit
     - Soda lime is used to recycle the exhaled air
     - Soda lime + Trilene→ toxic gasses
       → Phosgene- Acute Respiratory Distress Syndrome
       → Dichloro acetylene- Neurotoxicity
   - Trilene is used in open-circuit

7. **Cyclopropane**
   - Highly inflammable like Ether
   - Given in closed circuits.
   - Avoided in electrocautery
   - Used in shock as it increases BP by stimulating the sympathetic nervous system
   - Cyclopropane shock: Sudden Cyclopropane withdrawal can cause a sudden fall in sympathetic activity leading to hypotension

Important Information

- Ketamine (IV) also stimulates the sympathetic nervous system
  - Inhalational gas used in shock- cyclopropane.
  - IV agent used in shock- Ketamine

8. **Halothane** 01:09:39
   - High B/G partition coefficient- Slow onset/recovery
   - Low MAC- High potency, low dose
   - Maximum muscle relaxant property
   - Maximum Bronchodilation
   - Maximum Uterus relaxation
   - Maximum Vasodilation

Storage

- Amber-colored, opaque bottle to protect from light
- A red vaporizer is added to detect leakage
- Bottles covered with rubber seal to prevent leakage
- Thymol preservative (mercury-containing) is added to prevent bacterial growth

- **Properties**

H	• High B/G partition coefficient
	  ○ Slow onset of action
	  ○ Slow recovery from anesthesia

A	• Asthmatic patient – due to its maximum bronchodilatory effect
L	• Liver toxic – Hepatotoxicity
O	• Orthostatic hypotension • Side effect: Cause max. Vasodilation
T	Thymol as preservative
H	• Hyperthermia (malignant): side effect • Sudden muscle contraction in genetically susceptible individuals due to sudden release of calcium from SER • Treatment: Dantrolene (muscle relaxant)

A	• Arrhythmias
	  ○ It sensitizes the heart to epinephrine/norepinephrine
	  ○ Contraindicated in: Pheochromocytoma (increases the action of epinephrine/norepinephrine in the heart)

N	• Non-explosive
E	• End uterine contractions – Tocolytic action • Used in pregnancy to delay child labor
I	• Increases ICP
P	• Postanesthetic shivering -heat loss due to vasodilation • Treatment: Pethidine

Halogenated anesthetics (Fluranes) 01:18:00

- **Mnemonic: My SIDE**

	MAC value	B/G partition coefficient
Methoxyflurane	0.16	11
Sevoflurane	2.05	0.6
Isoflurane	1.15	1.4
Desflurane	6	0.45
Enflurane	2.5	1.9

Methoxyflurane	• First flurane drug to be made • Maximum Fluoride content- Most nephrotoxic flurane • Not used nowadays as it has a slow onset of action • Methoxyflurane o Least MAC value, Most potent o Highest B/G partition coefficient, slowest action
Sevoflurane	• Fast onset/recovery • Preferred in children as it has a sweet smell • Stable in cardiac and neurological patients • **Side effects** o Soda lime reaction in closed circuit → Toxic form - Compound A: Nephrotoxic - Carbon monoxide: Anemia o Seizures: not common
Isoflurane	• Pungent smelling- Increased risk of laryngospasm • Cause Vasodilation o Used in anesthesia to produce controlled hypotension o Side effects: Coronary steal syndrome (also caused by Dipyridamole) → Coronary artery dilation • Desflurane o Highest MAC value, Least potent o Lowest B/G partition coefficient, fastest action → Desflurane>Sevoflurane
Desflurane	• Most Pungent smelling- Increased risk of laryngospasm • Soda lime reaction may occur
Enflurane	• Sweat smelling • **Side effects**: Seizures common

Comparison of Inhalational agents 01:25:29

Condition	Drugs
Cardiac output **Heart rate** **Blood pressure**	• Cyclopropane shows the maximum increase • Halothane (muscle relaxant) causes maximum reduction
ICP	Maximum increase by Halothane
Uterine relaxation	Increase by Halothane
Bronchodilation	Increased by Halothane> Sevoflurane
Sweet smell	Sevoflurane (max.) & Enflurane
Pungent smelling	• Desflurane • Isoflurane • Ether
Soda lime reaction	• Sevoflurane • Trilene • Desflurane

Inhalational agent of choice 01:28:12

Parameter	Agent of choice
Induction & maintenance of Anesthesia:	Sevoflurane
Asthmatics	• Halothane > Sevoflurane • Injectable: Ketamine
Renal failure	Desflurane
Cardiac disease	Sevoflurane > Isoflurane
Liver failure	Isoflurane
Neurosurgery	Sevoflurane
Daycare Surgery	Sevoflurane (Sweat smell) > Desflurane (pungent)

Intravenous General anesthetics 01:29:46

Thiopentone

- Also known as Sodium pentothal

MOA	• It is a Barbituric acid • Open GABA-A chloride channel in neurons (suppressed)

Properties	• Yellow colored powder
	• pH: Acidic
	  ○ Mixed with sodium bicarbonate in injection so pH becomes alkaline, around 10-11
	• Highly lipid soluble
	  ○ Redistribution/deposition into fats
	  ○ Ultra-short-acting GA is used for inducing GA and not for maintenance

Uses	• Inducing GA • Neuroprotective effect- used in treating Status epilepticus • Anti thyroid action
Contraindications	• **Mixing of Thiopentone** • Never mixed in acidic Ringer lactate as it forms an insoluble salt precipitate. • Arterial injection of Thiopentone is never given as it causes endothelial damage leading to thrombosis. o Management: → Do not remove the syringe → Plenty of Saline to flush out thiopentone → Heparin (Anticoagulant) + Streptokinase (thrombolytic) → Pain is managed by Lignocaine • All barbiturates are not given in Acute intermittent porphyria o Precipitates attack by increasing heme demand by CYP induction
Side effects	• Hypotension • Sedation + Amnesia o DOC: Narco Analysis test o AKA: **Truth serum** (Hyoscine is also used) • Double apnoea o Suppression of respiration due to pungent smell and causes respiratory depression by entering the brain

Etomidate

01:38:34

ROA	Most hemodynamically stable among intravenous GA- Least effect on HR/BP
Uses	• DOC: Myocardial disease (CHF, MI, Angina) • DOC: Hypotension- does not alter BP • DOC: Old Age/senile patients
Side effects	**Mnemonic: PNVC** • Painful injection • Nausea & vomiting • Vitamin C deficiency • Corticosteroid hormone deficiency o Inhibit synthesis of Corticosteroid in the adrenal gland o Causes, Adrenal insufficiency

Important Information

- Painful injection: Etomidate (most) > Propofol > Methohexitone > Thiopentone
- Ketamine is a painless injection as it has a strong analgesic effect

Methohexitone

01:42:03

- It is a barbiturate
- Reduce seizure threshold (Provoke seizures easily)
- DOC: **ECT** (Electroconvulsive therapy)
  - Depression

Other drugs used in ECT

- Thiopentone
- Etomidate
- Propofol (most commonly used)
- Ketamine
  - DOC: ECT with depression
  - An inhalational nasal spray is Esketamine- approved in treating depression

Propofol

01:44:41

- The most commonly used GA

MOA	• Opens GABA-A chloride channel • Opens glycine chloride channel • Block excitatory neurotransmitter- NMDA antagonist
Properties	• Propofol solution is made in **milky white emulsion** and contains Soya bean, Egg white, and glycerol • Earlier believed, should not be given in egg allergy ○ Now accepted • Propofol solution must be prepared freshly every time and used within 6 hrs or else it could increase bacterial growth due to the presence of Soya bean, Egg white, Glycerol • **Fos-propofol**, additional phosphate group- More water-soluble and faster-acting
Uses	• DOC: Induction + maintenance GA • Mnemonic: Day TIME • DOC: Daycare surgeries • DOC: TIVA (Total Intravenous Anesthesia) • DOC: ICU patients • DOC: Malignant hyperthermia (Halothane causes Hyperthermia) • Antiemetic effect

Side effects	• Painful injection as it is an oily emulsion
	  ○ Etomidate (most painful)
	• Pancreatitis
	• Opisthotonus- Abnormal movement of the body
	• Pleasurable effect
	• PRIS (rare)- Propofol Related Infusion Syndrome
	  ○ Inhibits enzymes of mitochondria, ETC (Electron Transport System) causing decrease in oxygen production
	  → Cardiac failure
	  → Myopathies
	  → Liver failure

Ketamine

01:54:04

Structure	• Phenyl cyclidine derivative- Causes Hallucinations/psychosis • Dream like state • Also known as Angel dust (smuggler) • Misused as: Date Rape drug

MOA	• NMDA receptor antagonist- Blocks Glutamate receptors
	  ○ Produces Dissociative Anesthesia (Conscious Anesthesia)
	  → Loss of consciousness
	  → Normal reflex response
	  → GAG reflex (protective) preserved- prevents aspiration
	  ○ Can be used to perform surgery on a patient with full stomach
	• Strong pain-relieving action
	  ○ Analgesic effect
	  ○ Injection is painless
	• Increases sympathetic activity
	  ○ DOC: Shock, as it increases BP, HR
	  ○ DOC: Asthmatics as it causes bronchodilation

Side effects	**Mnemonic: VICE**
	• Vivid dreams/Hallucinations
	  ○ Contraindicated in Schizophrenia
	• Increase ICP/IOP
	  ○ Contraindicated in Glaucoma (IOP), head injury patients (ICP)
	• Cardiac output is increased
	  ○ The oxygen demand of the heart is increased
	  ○ Contraindicated in MI, Angina patients
	• Epilepsy
	  ○ Contraindicated in seizures

Comparison of Intravenous GA

02:01:38

	Thiopentone	Etomidate	Propofol	Ketamine
Half-life	Longest	→	→	Shortest
Nausea/vomiting		Max. Induction	Antiemetic	
Blood pressure	Reduce	Reduce	Max. Reduce	Increase
Cardiac output	Reduce	Reduce	Max. Reduce	Increase
ICP	Reduce	Reduce	Max. Reduce	Increase
IOP	Reduce	Reduce	Max. Reduce	Increase
Resp. rate	Reduce	Reduce	Max. Reduce	Increase
Painful injection	Painful	Most painful	Painful	Painless

Adjunctive drugs to GA

02:04:14

Dexmedetomidine

- Similar to clonidine
- Alpha 2A receptor agonist in CNS and reduces sympathetic activity
- Uses: Sedation, analgesia is produced perioperatively

Benzodiazepine

- Anterograde amnesia (loss of memory), Anxiolytic
- Mnemonic: DLMR
  - Diazepam
  - Lorazepam
  - Midazolam
  - Remimazolam

Anticholinergic drugs

- Reduce laryngeal secretions
- Mnemonic: HAG
  - Hyoscine
  - Atropine
  - Glycopyrrolate

Opioids

- Postoperative pain reduction
- Morphine, Fentanyl

Prokinetics

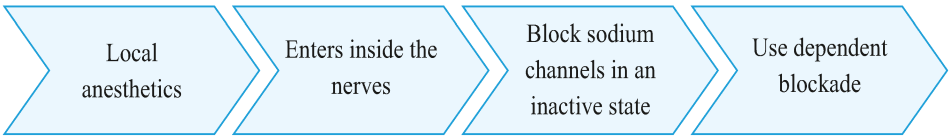
- Closes lower esophageal sphincter
  - Prevent aspiration into the lungs
  - Increases gastric emptying
- Metoclopramide, Domperidone

36 LOCAL ANESTHETICS

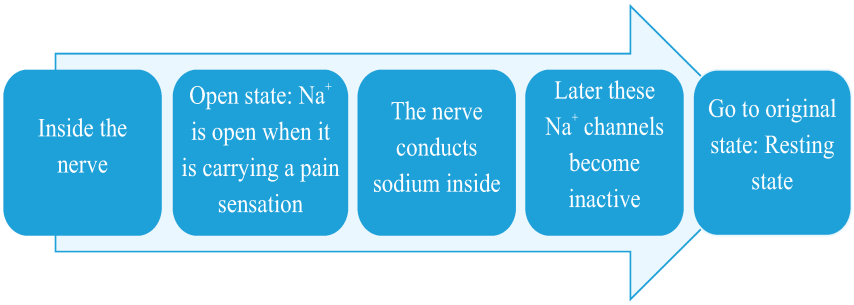
- **Anesthesia:** Reversible loss of sensation
- Local anesthetics block peripheral nerves
  - No loss of consciousness
- General anesthetics block nerves in the CNS
  - Loss of consciousness

Mechanism of action

00:01:40



Use Dependent Sodium Channel Blockage



- Local anesthetic acts inside the nerve by blocking the open or inactive Na^+ channels prolonging the resting state.

Properties of local anesthetics

00:05:53

- High lipid-soluble drugs cross cell membranes easily to produce a good effect.
- LA are weak basic drugs which means they have increased lipid solubility.
- Adding sodium bicarbonate (highly basic) makes the LA more lipid soluble thereby having a higher potency and longer duration of acting.
- Bicarbonate is not given with Bupivacaine as it is insoluble in bicarbonate

Local anesthetics

00:08:21

- LA with adrenaline with a concentration of 1:2 lakh produces vasoconstriction.
  - Reduces absorption of LA in blood
  - Decreased toxicity of LA
  - Increased duration of action
  - Decreased risk of bleeding
- **Contraindications of adrenaline with LA**
  - Tip of an organ surgery, adrenaline with LA is not used as they have end arteries that can lead to vasoconstriction, ischemic necrosis, and dry gangrene.
    → E.g. Finger surgery, Pinna surgery, Penile surgery, Nose tip surgery
  - Hypertension, heart disease
- Felypressin is an alternative to Adrenaline

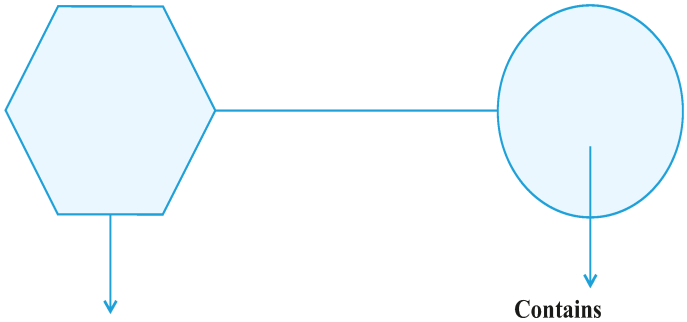
Differential sensitivity of Nerve fibers to LA

00:12:52

- Most susceptible to least susceptible
  - Autonomic > sensory > motor
  - Small diameter > large diameter
  - Myelinated > Unmyelinated.
- Order of sensitivity: A > B > C
- A fibers
  - Aγ > Aδ > Aβ > Aα
  - Aγ: Muscle tone
  - Aδ: Pinprick
  - Aβ: Touch
  - Aα: Motor
- B fibers: preganglionic sympathetic nerves
- C fibers: temperature (Last sensation to be lost)
- Bupivacaine shows the maximum property of differential sensitivity

Structure of Local Anaesthetics

00:17:02



Benzene-like ring called hydrophobic aromatic ring that blocks sodium channel

Contains

- Ester group or
- Amide group

Classification of local anesthetics

Ester containing LA: 1i

- Cocaine (1st LA natural)
- Procaine (1st synthetic LA)
- Chloroprocaine (Shortest, least potent)
- Tetracaine
- Benzocaine

Amide containing LA: 2i

- Lignocaine/Lidocaine/Xylocaine
- Articaine
- Mepivacaine
- Bupivacaine
- Prilocaine
- Etidocaine
- Ropivacaine
- Dibucaine – Longest, most potent

	Ester LA	Amide LA
Duration of action	Short-acting	Long-acting
Metabolism	Rapidly metabolized by plasma esterase	Metabolized in the Liver and degraded by amidase
Exception to metabolism	Cocaine is metabolized in the liver	Articaine is metabolized in the plasma
In liver disease	Safe	Unsafe
Risk of allergy	High	• Least risk • More commonly used

Esters LA

00:18:36

Cocaine

- 1st and the only natural LA
- Sourced from a plant called Erythroxylum coca
- Not used as LA by injection as it is highly addictive
- Sometimes used as eye drops in ocular anesthesia
- It is banned drug for use as a local anesthetic
- Cocaine addiction is treated by Topiramate and Gabapentin
- Only LA increases sympathetic activity (Sympathomimetic activity)
- Increase the release of epinephrine, norepinephrine – Sympathetic discharge is increased
- Only LA to produce vasoconstriction
- All other LA produce vasodilation

Procaine

- 1st synthetic LA
- DOC in malignant hyperthermia as lignocaine is contraindicated
- Procaine penicillin is a longer – acting drug

Chloroprocaine

- Shortest, least potent drug
- Converted to sodium metabisulphite leading to neurotoxicity
- Contraindicated in spinal anesthesia

Tetracaine

- Longer acting

Benzocaine

- Can be applied on cut surfaces due to minimal absorption

Amide LA

00:32:29

Lignocaine

- The most commonly used LA
- Also known as lignocaine, xylocaine
- It is also known as All-purpose LA
- Use
  - Topically on skin/mucous membrane. E.g. Foley's catheter insertion
  - A pure form of lignocaine is used in intravenous regional anesthesia- Bier's block
  - Epidural: Between dura mater and ligamentum flavum
  - Spinal: In CSF, between piameter & arachnoid mater
  - Nerve block or plexus block: Around a plexus
- Lignocaine cannot penetrate intact skin
- A special mixture known as EMLA can penetrate intact skin
  - Penetrate intact skin

Preparation	Lignocaine concentration
Intravenous regional anesthesia	0.5%
Nerve blocks	1-2%
Epidural	1-2%
Topical	2-4%
Spinal	5%

EMLA

00:37:07

- Eutectic mixture of local anesthetic
- Lignocaine (2.5%) + Prilocaine (2.5%)
  - Common melting point reduces and penetrates the intact skin
- Uses: needle phobia, skin grafting, atopic dermatitis
- Contraindicated in neonates as prilocaine causes methemoglobinemia.

Lignocaine toxicity

00:40:09

- Neurotoxicity- Most common
  - Perioral numbness first manifestation
  - Tremors
  - Seizures
  - Respiratory depression
  - Cardiac arrest
- Cardiotoxicity
- Malignant hyperthermia

Management of Lignocaine toxicity

Anaesthesia

- Midazolam, diazepam to control seizures or tremors
- Antidote for all LAs including lignocaine is 20% intra-lipid injection

Prilocaine

- Intravenous regional anesthesia (IVRA/ Bier's block)
- Lignocaine and Prilocaine are used in IVRA
- Bupivacaine is contraindicated in IVRA as it is the most cardiotoxic drug
- Side effect: Prilocaine is converted to Q- toluidine which causes methemoglobinemia.
- Contraindicated in neonates

Articaine

- Used in dental surgery

Etidocaine

- Contraindicated in dental surgery as it increases the risk of bleeding

Dibucaine

- Longest acting and most potent
- Used for diagnosis of pseudocholinesterase deficiency
- Also known as the Dibucaine number
  - For succinylcholine

Bupivacaine

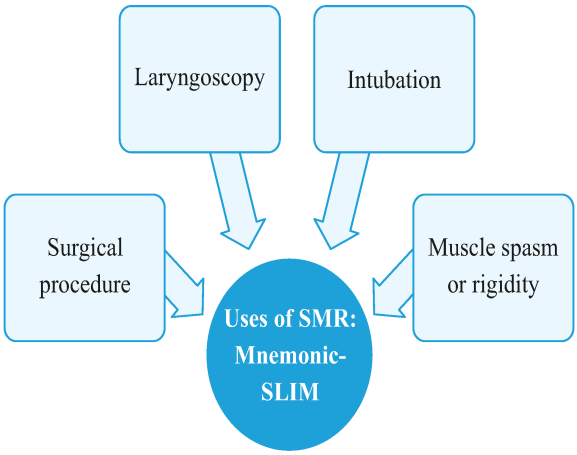
00:47:12

- Longer-acting than lignocaine- 2-3 hrs
- Most preferred in spinal anesthesia
- Maximum differential blockage of nerves
  - Blocks sensory > motor neuron
  - Used during labor
- Most cardiotoxic- never given IV (IVRA/ Bier's block) as it causes cardiac arrythmias
- ECG: Bradycardia
  - Treated by atropine
- Fibrillation
  - Treated by Amiodarone
- Antidote for Bupivacaine- 20% intralipid injection
- Levo - Bupivacaine- less cardiotoxic and more potent

Ropivacaine

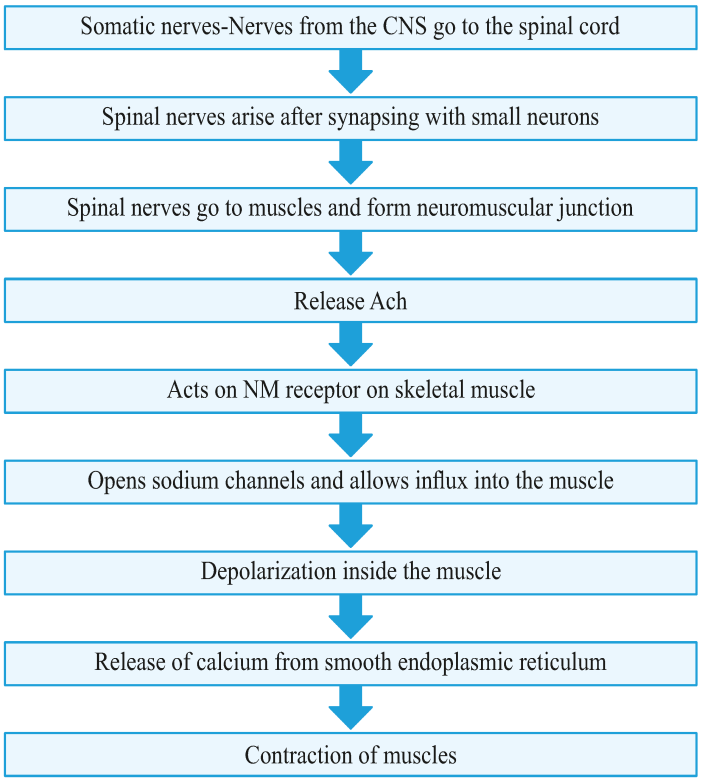
- Modified form of Bupivacaine
- Less cardiotoxic
- Can be given IV- IVRA/ Bier's Block

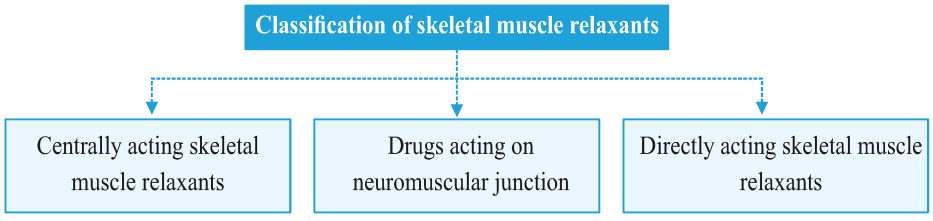
37 SKELETAL MUSCLE RELAXANTS



Contraction of a Muscle

00:01:24





Centrally Acting Skeletal Muscle Relaxants

00:04:40

- Acts on GABA-A chloride channel and α_{2A} receptor in the brain
- Acts on GABA-B receptor in the spinal cord

Benzodiazepines

Drugs and their MOA

- Diazepam, Nitrazepam:GABA-A Cl^- channel agonist
- Tizanidine: α_{2A} agonist
- Baclofen: GABA-B receptor agonist

Uses

- Decerebrate rigidity (Baclofen is not effective)
  - Stroke
  - Cerebral palsy
- Tetanus
- ALS
- Spinal injury
  - All 3 drugs are effective
- Sedating: Diazepam, Tizanidine
- Non-sedating: Baclofen

Mephenesin Group

MOA

- Blocks internuncial neuron (neuron present between the CNS and spinal cord)
- Internuncial neuron causes reflex muscle spasm- sudden spasms are seen in torticollis, muscle sprain, bursitis

Uses

- Treats localized muscle spasm

Drugs

- Mephenesin
- Methocarbamol
- Carisoprodol
- Chlorzoxazone

Directly Acting SMR

00:12:42

- Blocks sodium channels directly inside the muscle

Quinine

- DOC for nocturnal leg cramps

Dantrolene

MOA

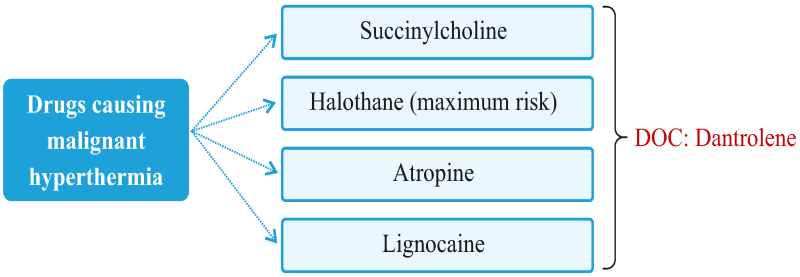
- Blocks SERCA-2 (smooth endoplasmic reticulum calcium channel)
- These channels are also known as ryanodine receptors

Uses

- DOC for malignant hyperthermia
  - Extreme rigidity leading to hyperthermia
  - Lactic acidosis leading to respiratory depression due to pulmonary edema
  - DIC

ROA

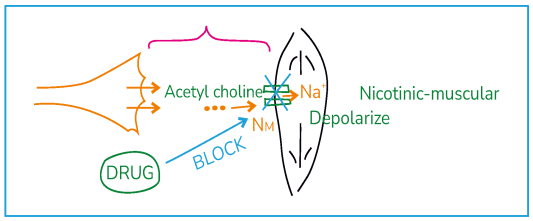
- Oral or IV
- It is an orphan drug



Drugs Acting on Neuromuscular Junction

00:19:02

- Blocks Nm receptor of Ach



PYQ: NEET PG 2022

Drug-Resistant TB

Depolarizing blockers

Suxamethonium/ succinylcholine
Decamethonium

Non-depolarizing blockers

(Used as poison by South American tribe) curare, curonium, curium

Steroidal: Curonium

Mnemonic: PVR

- Pancuronium
- Pipecuronium
- Vecuronium
- Rocuronium
- Rapacuronium

Benzo isoquinoline:Curare, Curium, Curine

Mnemonic: Tea Madam G

- Tubocurare
- Mivacurium
- Atracurium
- Doxacurium
- Cis atracurium
- Metocurine
- Gantacurium

Gallamine

- Not used
- Nephrotoxic
- Teratogenic

	Depolarizing Blockers	Non-Depolarizing Blockers
Drugs	Suxamethonium/ succinylcholine	Curonium, curium, curare

MOA	**Phase1**
	• Opening of Nm receptor (like Ach)
	  ○ Initial muscle contraction-Fasciculation
	  ○ Depolarizing SMR
	Enters into phase 2
	• Desensitization of the Nm receptor leads to flaccid paralysis of the muscle
		• Competitively block Nm receptor of Ach
		  ○ They are non-depolarizing and cause flaccid paralysis

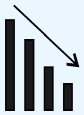
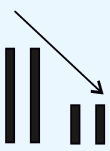
Role of Neostigmine	• Neostigmine cannot reverse the effect of succinylcholine	• For reversal of NDMR: increase Ach
		  ○ Neostigmine
		  ○ Edrophonium

Initial Fasciculations	Yes	No
Postoperative myalgia	Yes	No
Reversal by Neostigmine	No	Yes
Cold Temperature	Increase the effect	Decrease the effect
Muscle sensitivity	1st to paralyze: Neck muscle Last to paralyze: Diaphragm (Most resistant, 1st to recover)	1st: Fingers Last: Diaphragm

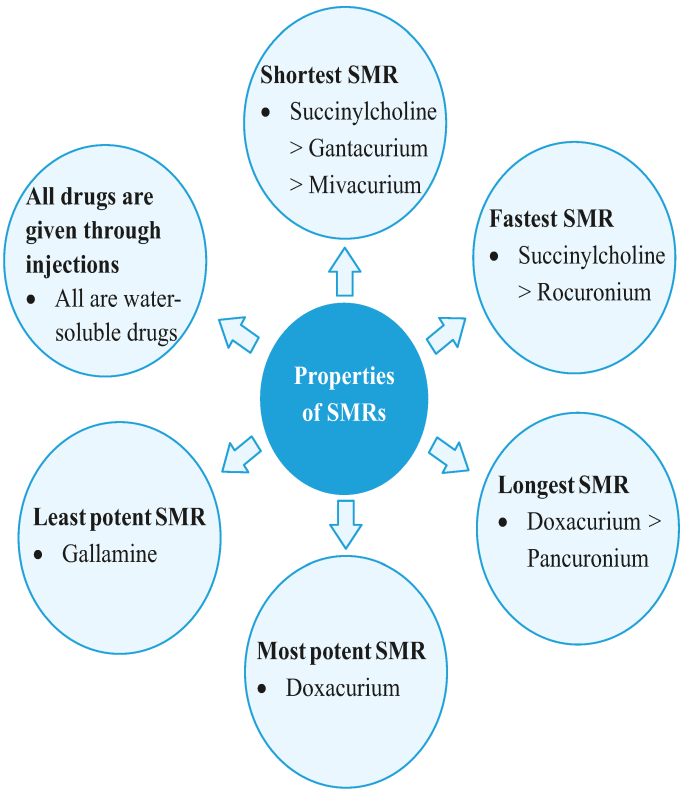
Assessment of Effect of SMR

00:34:26

- To assess the effect of SMR, nerves are stimulated by electric current. E.g.
  - Ulnar nerve: Adductor pollicis
  - Facial nerve: Orbicularis oculi

	Normal EMG	Depolarizing blockers	Non-depolarizing blockers
Train of 4 4 electrical stimuli are given at a frequency of 2 Hz each		Weak contraction Reduced intensity 	Fading happens 
Double burst stimulus 2 stimuli of 50Hz each and after 750 msec, 2 stimuli are repeated		Less intensity in depolarizing blockers 	Fading happens 

Post tetanic potentiation • 50Hz stimulus is given continuously for 5 sec (tetanic manner) and after a gap of 1 sec the stimulus is repeated		Intensity is reduced 	Fading occurs but after 1 sec as ACh stores are repleted, they will produce good muscle contraction



00:44:09

Succinylcholine and Mivacurium
- Metabolism by pseudocholinesterase (plasma enzyme)
- This enzyme is also known as butyrylcholine esterase

Gantacurium
- Cysteine adduction

Metabolism and Excretion — PYQ: INICET 2023

Atracurium
- Hofmann elimination (1/3) + plasma esterase (2/3)
- Spontaneous inactivation by molecular rearrangement
- Safest in hepatic & renal disease

Cis atracurium
- Hofmann elimination (100%)
- Safest in hepatic & renal disease

All other SMRs are metabolized in the liver and excreted through the kidney into the urine.

- Exceptions
  - Rocuronium is contraindicated in obstructive jaundice as it is eliminated only in bile and not in urine.
  - Doxacurium is only eliminated in urine

Atracurium Vs Cis Atracurium

00:49:49

Atracurium	Cis Atracurium
Mixture of >10 isomers	Only 1 isomer
Metabolised by Hofmann elimination and plasma esterase	Metabolised by Hofmann elimination (100%)
Histamine release leading to allergy	No histamine release
Laudanosine is a toxic form that accumulates in renal failure leading to a high risk of seizures	Not seen

Histamine Release by SMR

00:52:30

Drugs producing histamine release	Clinical feature of histamine release

• D- tubocurarine has the maximum histamine release
• Atracurium
• Mivacurium
• Succinylcholine
	• Anaphylactoid reactions
	  ○ Flushing
	  ○ Hypotension
	  ○ Asthma

Action on Autonomic Ganglia (Nn receptor)

- Nn receptor present between pre-ganglionic and post-ganglionic
- Succinylcholine stimulates Nn receptor causing bradycardia due to vagomimetic effect.
- Tubocurare causes maximum blockage of Nn receptors causing tachycardia due to the vagolytic effect
- Vecuronium does not affect Nn receptors, hence no effect on the heart.
  - It is a cardio-stable SMR
  - DOC in heart disease

Succinylcholine

00:57:59

Also known as

- Suxamethonium / Scoline

Duration of action

- Fastest, shortest acting
  - Action starts in 30 seconds
  - Duration: 3-8 mins

Uses

- Used in intubation
  - Succinylcholine
  - Mivacurium
  - Rocuronium

Chemical Structure

- Dimer of acetylcholine

Storage

- Storage: 2 years
- Temperature: 2-8^{0}C

Metabolism

- Metabolism by pseudocholinesterase
- Pseudocholinesterase is deficient in 20% of the patients
- In atypical variety of pseudocholinesterase
  - Cannot inactivate succinylcholine leading to toxicity causing diaphragm paralysis called Scoline apnea

Dibucaine Number

- Used to check whether pseudocholinesterase is of normal variety or atypical variety.
- Dibucaine is a local anaesthetic that can inhibit typical or normal pseudocholinesterase and reducing its activity by 80%
- Atypical variety of pseudocholinesterase activity is reduced only by 20%

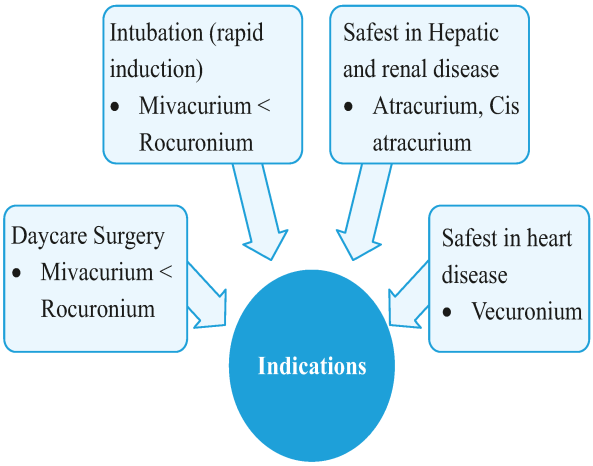
01:05:41

Toxicity of Succinylcholine

- Scoline apnea
- Hyperkalemia
  - Due to potassium release that can lead to cardiac arrest
  - Increased in trauma, burns rhabdomyolysis
- Malignant hyperthermia
  - Treated by Dantrolene

Contraindications

- Muscle dystrophy
- Neurological disease
  - Hemiplegia
  - Stroke
- Contraindicated in head injury, glaucoma
  - Increases ICP, IOP



Reversal of Effect of NDMR

- DOC: reversal agents (Increases Ach)
  - Neostigmine
  - Edrophonium
  - Add atropine to block the muscarinic receptor.
- **New drug**
  - Sugammadex- Reversal agent only for Rocuronium and Vecuronium
  - Sugammadex is a gamma-cyclodextrin.
  - It directly binds to Rocuronium and Vecuronium inhibits their actions on Nm receptors.